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The Journal of Allergy

VOL. 16 SEPTEMBER, 1945 No. 5

American Academy of Allergy

First Annual Meeting, New York, N. Y., Dec. 11 and 12, 1944

(Continued)

ATOPY TO SIMPLE CHEMICAL COMPOUNDS—SULFONECHLORAMIDES*†

SAMUEL M. FEINBERG, M.D., AND ROBERT M. WATROUS, M.D., CHICAGO, ILL.

OUR attention was attracted to a situation in a pharmaceutical factory where a number of workers were experiencing symptoms of asthma and hay fever on inhaling small amounts of the dust of two organic substances, chloramine-T and halazone. These workers generally became sensitized while working in the department in which these chemicals were manufactured or packaged. When removed from that division of the factory they were relieved of their symptoms under most circumstances until about three years ago. Unprecedented demand in recent years for these substances by the Armed Forces for purposes of water-disinfection has resulted in unusual manufacturing conditions. The exhaust of some of the dust into the outside air has contaminated the latter sufficiently so that most of the sensitized persons stationed in other buildings as far as 300 yards away experienced respiratory symptoms when the wind blew from the direction of the chloramine factory.

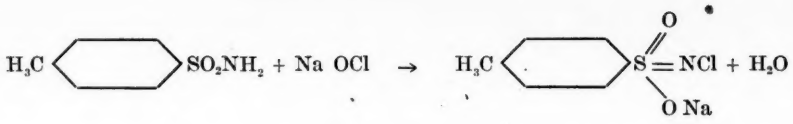
When we began to investigate the first case, the question naturally arose whether or not we were dealing with an example of a chemical irritant of sufficient intensity to disturb equilibrium in a person who is atopic to other substances. Since it is a commonly accepted concept that chemical irritants, such as sulfur dioxide, gasoline fumes, and chlorine can precipitate atopic symptoms as nonspecific excitants, it was but natural to assume that the chloramides acted in much the same manner. The preliminary investigation on the first patient, however, produced findings which definitely indicated that we were dealing here with a specific allergic phenomenon. We decided, therefore, to make a study of the other patients and of the problem in general.

MANUFACTURE AND EXPOSURE

Chloramine-T (Chlorazene) is prepared by treating *p*-toluene sulfonamide with sodium hypochlorite:

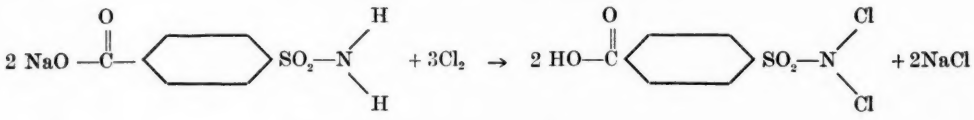
*From the Division of Allergy, Department of Medicine, Northwestern University Medical School and the Plant Physician's Department of Abbott Laboratories.

†Read before the First Annual Meeting of the American Academy of Allergy, New York, Dec. 11, 1944.



The finished product is a white solid which has a strong smell of chlorine; it is readily soluble in water. It is mixed with excipients to be made into tablets or placed in packages as a powder. In manufacturing chloramine-T the material is dried, ground, mixed, compressed into tablets, and packed. All of these operations are accompanied by the escape of dust into the air, and for many years it was common knowledge among the workmen who handled this drug that it often produced symptoms resembling those of the common cold. There might be sneezing, rhinorrhea, nasal obstruction, lacrimation, or cough. It was known that some individuals were more severely affected than others.

Halazone (*p*-sulfonedichloramidobenzoic acid) is prepared by treating sodium *p*-sulfonamidobenzoate with chlorine in alkaline solution:

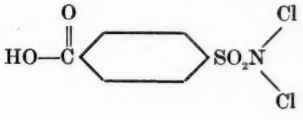


It is a white powder which is practically insoluble in water and has a strong odor of chlorine. Much the same operations must be performed on this chemical to put it in a suitable form for medicinal use, but in the preparation of the pure compound the symptoms experienced by the workmen are chiefly those which would be caused by the chlorine gas itself; there is less sneezing, more bronchial irritation, and the lacrimation is accompanied by more signs of chemical irritation than in the case of chloramine-T. Dust from the purified chemical gives relatively few symptoms. When pure halazone powder is mixed with sodium borate and sodium chloride its solubility is markedly increased, and the dust from the mixture has markedly increased irritative effects, even though the halazone content is reduced by dilution. When this mixture is compressed into tablets the dust created by the machines may produce follicular dermatitis, rhinitis, conjunctivitis, keratitis, tracheitis, and bronchitis. These symptoms appeared in a number of workmen who tended the machines, and their severity was, in general, proportional to the length of exposure. One measurement made of the dust content of the air in this workroom showed it to contain 0.03 mg. of active chlorine per cubic foot. This would correspond to 0.12 mg. of pure halazone or 3.84 mg. of the tablet mixture. Thus, a workman, unprotected by a mask, could inhale about 14 mg. of pure halazone dust in eight hours. Women who counted the tablets and placed them in bottles were also exposed to dust, but to a much less marked degree; nevertheless, many of them complained of nasal and bronchial irritation, and a number manifested the follicular dermatitis. Among the workers affected, however, a small group stood out because of their progressively decreased tolerance to the dust. Their symptoms at first had the character of primary irritation, and were proportional to the degree of exposure; soon, however, the bronchial irritation was transformed into a picture of dyspnea, a sense of oppression in the chest, and finally into typical bronchial asthma. With this change in symptoms, the amount of exposure necessary to produce the attacks decreased more and more, until finally the slightest trace of dust

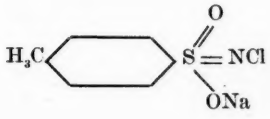
might provoke an attack. Recognition of this complication led to the installation of elaborate dust-collecting systems until contamination of the air was reduced below the threshold of primary irritation. This prevented the outbreak of new cases, but those in whom the sensitivity had been established were not able to work anywhere in the vicinity of halazone or chloramine-T without the danger of asthmatic seizures.

SKIN TESTS

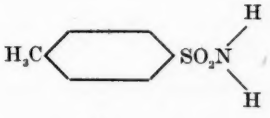
The first patient we investigated (P.N.) gave marked immediate whealing reactions by scratch test with solutions of chloramine-T and halazone up to and including the 1:100,000 dilution. Numerous control subjects failed to react with the most concentrated solutions by scratch test and with as high a concentration as 1:1,000 endermically. This finding in the first patient led us to an investigation of five additional subjects whose histories suggested sensitivity to these substances. The fact that halazone and chloramine-T behave as true atopens offers a unique opportunity to study the relation of chemical structure to the allergic mechanism. Both compounds have a known, relatively simple molecular structure, and substances differing from them only in slight detail are easily available. With the help of M. B. Moore, Ph.D., a list of compounds differing from these two chloramides only with respect to one or two chemical groupings was selected. The following are their structural formulas:



Halazone (*p*-sulfonedichloramidobenzoic acid)

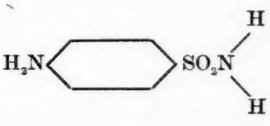


Chloramine-T (sodium *p*-toluenesulfonechloramide)



p-Toluenesulfonamide

Sodium *p*-toluene sulfonate

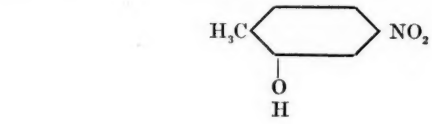


p-Aminobenzenesulfonamide (sulfanilamide)

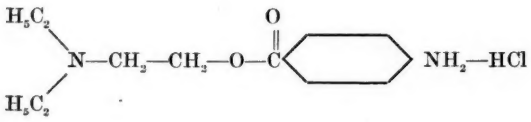
p-Aminobenzoic acid

To test separately the groups $-SO_2-$ and $-OCl$, solutions of sodium sulfite and sodium hypochlorite were used, since these radicals cannot otherwise exist in an aqueous solution containing the sodium ion.

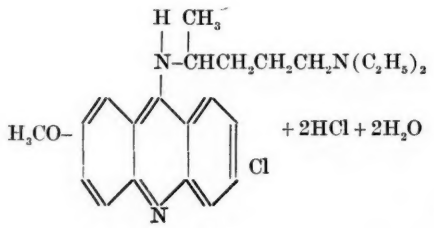
For purposes of skin testing, all the compounds of the first group were made up in solutions designed to be equimolar with respect to 1 per cent chloramine-T. The sodium sulfite was also prepared on this basis. The sodium hypochlorite solution was prepared by bubbling chlorine gas through 1 per cent sodium hydroxide solution. This, however, was found to be a primary irritant, and caused chemical corrosion of the skin in a control subject who did not react to any of the other solutions. Accordingly, skin tests were made with this solution in a dilution of 1:10. Some of the patients tested had been exposed to other chemicals which they believed might precipitate asthmatic seizures, and so all were tested with three of these:



m-Nitro-*o*-cresol



Procaine hydrochloride



Quinacrine dihydrochloride

M-Nitro-o-cresol was prepared in solution to be equimolar with 1 per cent chloramine-T; quinacrine dihydrochloride and procaine hydrochloride were used in 1 per cent solution.

Several of the chemicals used were not sufficiently soluble in distilled water to make solutions equimolar with 1 per cent chloramine-T. In such cases the amount theoretically required to make 100 ml. of the equimolar solution was weighed into a bottle. One hundred milliliters of distilled water were added, and the bottle was shaken at room temperature until the water would not take up any more solid. The solid was allowed to settle and skin tests were made with the supernate. Because of the solubilizing action of sodium borate and sodium chloride on halazone, which was very sparingly soluble by itself, tests were made both with the supernate from pure halazone and with a 1 per cent solution of halazone tablets (which contained 0.03 per cent of halazone).

In addition to these chemical substances tests were made also with the most important inhalant atopens commonly employed in testing cases of respiratory allergy. All tests were made by the scratch method. The findings are summarized in Table I.

It will be noted that of the simple chemicals only chloramine-T and halazone gave definite reactions. We realize, of course, that the list utilized in our tests does not exhaust all possible combinations of chemical structure and interspatial grouping. To learn more about the antigenic behavior of these substances further tests are being undertaken with a wider range of related chemicals.

TABLE I. SCRATCH TESTS ON PATIENTS IN FIRST GROUP

PATIENT		P. N.	F. M.	P. T.	L. L.	B. M.	H. S.
Sulfanilamide	0.756%	0	0	0	0	0	0
Chloramine-T	1.0	++++	+	++++	+	+	++
Chloramine-T	10.0	++++	++++	++++	+	+++	+++
Halazone	1.187	+	0	+	+	++	±
Halazone tablets	1.0	+++	++	++	++	++	+
p-Toluenesulfonamide	0.664	0	0	0	0	0	0
Sodium hypochlorite	0.1	0	0	0	0	0	0
Sodium *p*-toluenesulfonate	0.853	0	±	0	0	0	0
p-Aminobenzoic acid	0.602	0	0	0	0	0	0
Sodium sulfite	0.554	0	0	0	0	0	0
m-Nitro-*o*-cresol	0.677	+	0	0	0	0	0
Procain hydrochloride	1.0	0	0	0	0	0	0
Quinacrine dihydrochloride	1.0	0	0	0	0	0	0
Feathers		0	0	0	0	0	0
Cat hair		0	0	0	0	0	0
Cow hair		0	0	±	±	0	0
Dog hair		0	0	+	±	0	0
Horsehair		0	0	+	+	0	0
House dust		0	0	++++	0	0	+++
Cottonseed		0	0	0	0	0	0
Orris		0	0	0	0	0	0
Alternaria		0	0	0	±	0	0
Ragweed		0	+++	0	±	0	0
Timothy		0	+	0	0	0	0

After the preliminary skin tests on the six patients, whose histories will be detailed later in the paper, a survey was made of all persons in the factory who had ever complained of being sensitive to either of the two chloramides. This comprised a group of fourteen persons who suffered either from periodic attacks of asthma or from attacks of sneezing, rhinorrhea, and nasal congestion. Since the chemical substances related to chloramine-T and halazone had previously failed to show reactions and since chloramine-T was apparently the more active of the two chloramides, the latter only was used for testing this additional group of subjects. Scratch tests were performed on most of them with five strengths of chloramine-T in aqueous solution. In all cases one extra scratch was made to detect any tendency to form wheals from purely mechanical irritation. The results of these tests are recorded in Table II.

The fact that only eight out of this group gave strong positive skin reactions to chloramine-T is open to two possible interpretations: (1) The case histories, which were very suggestive, may have been exaggerated by the patients. (2) The scratch test may fail to diagnose all cases of clinical sensitivity: a dermal test might give a positive reaction in some of those who are recorded here as negative.

We thus have fourteen instances of asthma and rhinitis in which the history

TABLE II. SKIN TESTS WITH CHLORAMINE-T ON SECOND GROUP OF PATIENTS

		DILUTIONS OF CHLORAMINE-T				
PATIENT	CONTROL	1:10	1:100	1:1,000	1:10,000	1:100,000
H. H.	0		++++	±	0	0
W. W.	0		0	0	0	0
H. S.	0		++++	++++	++	±
T. W.	0		++++	++	0	0
J. K.	0		++++	+++	++	±
M. D.	0	±	0	0	0	0
E. P.	0	+	0	0	0	0
L. M.	0	±	0	0	0	0
A. L.	0	++++	++++	+++	±	0
C. T.	0	0	0	0	0	0
S. B.	0	±	±	±	0	0
W. D.	0	+	0	0	0	0
I. S.	0	0	0	0	0	0
C. C.	0	++++	++++			

and a definitely positive and specific skin reaction indicate an atopic sensitivity to the sulfonechloramides. Another instance of asthma with positive skin reactions, in a physician who handled halazone, has been reported to me.[1]

ATOPIC REAGINS

A search for the presence of reagins was made in the blood of six of the patients in the first group. For routine study two recipients were used and tests were made with solutions of chloramine-T, 1:100,000, 1:10,000, and 1:1,000 on the sensitized sites. The sera of four patients gave definite and repeated positive reaction with the 1:1,000 solution of the chemical, two gave reactions with the 1:10,000 and one gave reactions with the 1:100,000 solution of choramine-T. All tests at control sites were negative. The results are recorded in Table III. It is possible that if higher concentrations of the chemical could be used for endermic testing, reagins might be demonstrated in the remainder.

TABLE III. PASSIVE TRANSFER

	DILUTIONS OF CHLORAMINE-T					
PATIENT	1:100,000		1:10,000		1:1,000	
	Recipient A	*Recipient B*	*Recipient A*	*Recipient B*	*Recipient A*	*Recipient B*
P. N.	+	+	+	+	+++	+++
F. M.	0	0	0	0	0	0
P. T.	0	0	0	0	++	++
L. L.	0	0	0	0	0	0
B. M.	0	0	0	0	+	+
H. S.	0	0	+	0	++	+

STABILITY OF ANTIGEN

One of the first points to be investigated in relation to these atopens concerned their stability. This question seemed important for two reasons? (1) In planning to attempt desensitization of patients and to conduct immunologic experiments it would be necessary to know whether this substance is extremely unstable as an antigen or whether a solution would keep for a reasonable period. (2) The information was wanted for further study toward an understanding of the chemistry of the antigen. Since in our previous clinical trials it was apparent that the chlorine atom was necessary for the activity of this antigen and since these substances give off some clorine when they are in solution, it was feared that the antigenic properties would be lost rapidly.

The question was studied by two methods. Chloramine-T was made up in serial dilutions at one time. At varying intervals, of a day, a week, and several weeks, scratch tests were made on one of the most sensitive patients (P. N.) From the very beginning to the end of the period the patient showed positive reactions to the same dilutions, with an endpoint of 1:100,000. A similar study was made by the passive transfer method. Serum from the same patient was lyophilized in a number of tubes. At intervals the freshly redissolved lyophilized serum was used in sensitizing a series of cutaneous sites on the same subject, and tests were made with dilutions of chloramine-T prepared at the beginning of the experiment. The results are shown in Table IV.

TABLE IV. STUDY ON STABILITY OF ANTIGEN BY PASSIVE TRANSFER

CHLORAMINE-T DILUTIONS	4/27/44	5/2/44	6/6/44	8/1/44
1:10,000,000	0	0	0	0
1:1,000,000	0	0	0	+
1:100,000	+	+	+	+
1:10,000	++	++	++	++

After more than three months no loss of allergenic potency could be demonstrated. We realize, of course, that both the direct and passive transfer tests afford only a rough estimate of antigenic potency, but for practical purposes we can conclude that even weak solutions of chloramin-T atopen undergo no pronounced loss of potency after three months.

Attempts at desensitization indicate clinically and immunologically that the behavior of this atopen is identical with that found in desensitization with atopens of high molecular weight. We shall report on this phase of the subject at another time.

For the sake of brevity the salient points in the histories of the chloramine sensitive patients are summarized in Table V.

TABLE V. DATA ON PATIENTS REACTING TO CHLORAMINE-T

PATIENT	SEX	AGE (YRS.)	SYMPTOMS	DURATION (YRS.)	DURATION IN YEARS OF CHLORAMINE EXPOSURE PRIOR TO SYMPTOMS	ATOPY PRECEDING EMPLOYMENT	OTHER PRESENT ATOPY	FAMILIAL ATOPY	OTHER SKIN REACTIONS
P. N.	M	46	A-R	10	10	0	0	?	0
F. M.	F	57	A-R	3	15	+	+	0	+
P. T.	F	27	A-R	4	4	0	?	0	+
L. L.	M	35	A-R	6	3	0	0	0	±
B. M.	F	31	A-R	3	6	0	0	0	0
H. S.	M	30	A-R	4	½	0	+	+	+
H. H.	M	39	A	7	10	0	0	0	+
H. S.	F	26	A	1	6	+	?	?	
T. W.	M	38	A-R	8	2	+	+	0	
J. K.	M	45	A-R	7	18	0	0	0	
E. P.	F	31	R	1½	3	0	0	0	
A. L.	F	28	A-R	4	5½	0	0	+	+
W. D.	M	52	C	½	¾	0	0	0	
C. C.	M	66	A	6	?	+	0	0	

A = asthma.
R = rhinitis.
C = cough.

Examination of the table shows that four out of the fourteen patients gave a history of atopic symptoms previous to exposure to the chloramines. A definite family history of atopy was present in two and questionable in two others. In at least three of the group there was evidence of associated allergic complaints which could not be attributed entirely to the chemicals. It is very likely that the incidence of a personal or family history of atopy in this group is underestimated, because of the general inclination of industrial workers to minimize such facts in connection with their occupational illnesses. Skin tests with atopens other than the chloramides were done on nine patients, in five of whom definite reactions were obtained. From the preceding results one can reasonably assume that although the chloramides are chemicals which may be regarded as potent sensitizers, it is primarily the individual with the atopic constitution who is apt to acquire such sensitivity. Since these facts have been brought to light, persons with a history of personal or familial atopy have not been accepted for employment in that particular branch of the factory.

An attempt was made to estimate the duration of exposure to the chloramides prior to the onset of recognizable allergic symptoms. It will be noted that such periods ranged from six months to eighteen years. In the last case in

Table V (C. C.) there was no evidence of intimate occupational contact with chloramides. This patient apparently acquired his sensitization from the slight atmospheric contamination on the grounds, from the clothes of workers, or from similar indirect exposure.

CASE REPORTS

CASE 1.—P. N., an East-Indian man, 46 years of age, began work in the chemical manufacturing division of the pharmaceutical plant twenty-one years ago, and has worked there ever since. The only instance of allergic disorder the patient could recall in his family was a specific sensitivity exhibited by his mother to a particular fruit which was harmless to others, but which produced violent gastrointestinal symptoms whenever she ate it. The patient himself never suffered from hay fever, eczema, urticaria, or asthma in early life. He was exposed to many irritating chemicals, dusts, and vapors during the first five years of his employment but never noticed any more reaction than was common to other workers. Sixteen years ago, he inhaled large amounts of dibutylamine, an intense local irritant, and following this he developed very severe rhinitis and sinusitis. When the acute symptoms subsided, he found he had completely lost his olfactory sense; this loss lasted about two years. Ten years ago, the patient happened to walk into a room where a quantity of chloramine-T was being sifted under very dusty conditions. He suffered an immediate attack of sneezing, coughing, hoarseness, sweating, and weakness. Prior to this attack, exposure to this dust had never affected him as far as he noticed, but from then on even slight traces would evoke mild attacks of sneezing; he suffered such attacks even when others were unable to detect any odor of chloramine-T in the air. Seven years ago, he was exposed to fumes of mandelic acid during its manufacture, and then noted for the first time a sense of difficult respiration, with wheezing. This never appeared except following exposure to mandelic acid. Finally, two years ago, the increased manufacture of halazone was accompanied by the discharge of dust from various ventilating systems into the outdoor air, and the patient began to notice attacks of dyspnea and wheezing respiration whenever he came near these exhaust ducts, or whenever the wind happened to blow in such a direction that the exhausted dust was carried toward his place of work. These attacks became more severe and more disabling over a period of months, but always disappeared when the patient spent a few days at home. Physical examination on Feb. 29, 1944, revealed a normally developed man, weighing 129 pounds and measuring 66 inches in height. The only abnormalities found were slight diminution of vision for distant objects, fully corrected by glasses, and a liver margin palpable about 2 cm. below the costal border on deep inspiration. The urine was free of albumin and sugar. Routine blood counts taken every three months for the past three years had been essentially normal except for occasional eosinophilia.

CASE 2.—F. M., a single white woman, 57 years of age, began work in the packing department of the pharmaceutical company eighteen years ago. There was no history of asthma or hay fever in the patient's family. She herself suffered from seasonal hay fever accompanied by dyspnea for many years, but was never prevented from working by this illness. During her long experience, the patient handled all varieties of drugs in the packaging department, and on many occasions was exposed to dust from chloramine-T (in tablet or powder form) or halazone. The first attack of asthma which came to the attention of the plant physician occurred three years ago, but the patient had at that time been under the treatment of a private physician and was taking medication. This first attack occurred while while she was at work in the packing department, and at that time no connection with any particular dust was noted. Rest, oxygen inhalation, and sympathomimetic drugs prescribed by the private physician produced relief. The next acute attack occurred when the patient was distributing pay checks in the packing department six months later. Three further attacks occurred in the next three months, and by this time the connection with the exposure to halazone dust in the packing department seemed a likely etiological factor; accordingly, the patient was transferred to another department. She remained relatively free from attacks for one year. Physical examination on Feb. 29, 1944, revealed a woman of small stature and build, weighing 98 pounds and measuring 60 inches in height. Distant vision was 7/20 in both eyes; the thyroid was slightly enlarged. The heart was normal in size, and the heart sounds were normal. Musical râles were audible throughout the chest, both on inspiration and expiration. Other physical findings were normal. The urine was free from albumin and sugar.

CASE 3.—P. T., a single white woman, 27 years of age, was first employed in the packing department of the pharmaceutical factory eight years ago. There was no history of allergy in the patient's family, and she stated she was free from any form of allergy herself until four years ago. At that time, she began to suffer from attacks of cough, dyspnea, irritation of the eyes, and sneezing, which she gradually came to recognize as being associated with exposure to dust while at work. By observation over a period of three months, she found that the dust of chloramine-T, to which she was occasionally exposed in the packing department, was the most powerful agent in producing these attacks. She found that attacks of sneezing were provoked by the proximity of other workers who had traces of the material on their workclothes. Between June and September of that year she lost 14 pounds, and thus finally reported her symptoms to the plant physician. She had already consulted a private physician, who had made a diagnosis of bronchial asthma and had prescribed oral medication. A complete physical examination at this time revealed a rather thin woman weighing 100 pounds and measuring 63 inches in height. Abnormal findings included a pulse rate of 100, blood pressure of 85/60, diminution of hearing for high-pitched sounds in the right ear, and the presence of musical râles throughout the chest. During the rest of the year, the patient was not allowed to work with chloramine-T, but continued in the same department; she reported only one asthmatic attack, and was noted on another occasion to have an urticarial eruption. The following year, several attacks of asthma occurred, and the patient attributed these to several substances encountered at work. She was transferred to another department two years ago, and made no further complaint of asthma for more than a year. About a year ago, when the production of halazone had greately increased, and the door of the room where the patient worked had been left open contrary to the usual custom, dust from halazone manufacture entered the room, and the patient had an asthmatic attack. In January, 1944, the patient was examined at the Lake County Tuberculosis Sanatorium by Dr. C. K. Petter. A tuberculin patch test gave a positive reaction, and a single roentgenogram of the chest revealed small calcified deposits in both hilar shadows; otherwise, the chest was negative.

CASE 4.—L. L., a married white man, 35 years of age, was first employed in the tablet- and capsule-manufacturing department of the pharmaceutical factory nine years ago. A cursory pre-employment examination revealed no abnormalities. There was no history of allergy in the patient's family, and the patient himself was free from any allergic symptoms until about five years ago. Six years ago, he developed signs of hyperthyroidism and underwent thyroidectomy. Following this, he was normal for a month, and then complained of attacks of coughing and sneezing, which he attributed to dust encountered in his work of filling hard gelatin capsules. He stated at the time that the most irritant dust was that of chloramine-T. During the next three months, these attacks continued, finallly culminating in attacks of dsynea which caused absence from work. A complete physical examination done at that time (five years ago) revealed a normally developed male 30 years of age, weighing 193 pounds and measuring 68 inches in height. Marked exophthalmos was present, and the only abnormal finding was a blood pressure of 140/80. A differential white count taken at this time was normal. Physical findings in the chest were normal at the time of examination. Stereoscopic roentgenograms of the chest revealed no evidence of tuberculosis a few months later. He was transferred from the tablet department to the shipping room, but soon began to complain of dyspnea and cough which he attributed to excelsior dust. Accordingly, he was transferred back to his former work. About three years ago, the patient was seen in the plant physician's department suffering from acute dyspnea, with wheezing respiration. He stated he had been exposed to dust from chloramine-T. Rest at home alleviated the symptoms, but return to work caused them to return. Administration of ephedrine gave relief. Despite transfer to various other departments, the patient continued to complain of dyspnea and cough, generally related to some accidental exposure to chloramine-T or other dust. The first objective sign of asthma was found on Dec. 9, 1941, when loud musical râles were heard in the chest. On this occasion, 0.5 ml. of epinephrine solution injected subcutaneously secured relief from dyspnea. A chest plate made the following day revealed slightly increased prominence of the linear markings, particularly in the lower lobes, with thickening in the hilar regions. The apices and lung fields were otherwise clear throughout. The heart, trachea, aorta, diaphragm, and bony framework of the chest were normal. The patient was treated with ephedrine and nembutal capsules, and was relatively free from symptoms during the year 1942. Early in 1943, he had another asthmatic attack, this time brought about by the proximity of other employees who had been working with halazone and whose clothing was heavily

contaminated with dust. The attack was relieved by an injection of epinephrine. Similar attacks occurred with increasing frequency throughout the year, and it was noted that the patient was becoming sensitive to almost any type of irritant; coal smoke, ammonia vapor, and benzyl chloride fumes provoked attacks at different times. He was finally placed in the stockroom of the machine shop but continued to complain of dyspnea, which he attributed to such irritants as fumes from arc-welding electrodes, acetylene gas, or foggy weather. In February, 1944, a carload of ammonia was unloaded near the machine shop, and fumes entering the shop caused considerable discomfort among all the workmen. On this occasion, the patient suffered an alarming attack of dyspnea, which could not be relieved by oxygen or injections of epinephrine. He was still slightly dyspneic three days later.

CASE 5.—B. M., a white woman, 31 years of age, began work in the packaging department of the pharmaceutical factory ten years ago. There was no history of allergy in the patient's family, and she herself never suffered from infantile eczema or hay fever. The only symptoms suggestive of allergy reported by the patient were occasional attacks of itching, without true wheal formation, following the eating of strawberries, and nausea on eating corn. The patient continued work in the packaging department for six years, being exposed from time to time, like all the other workers, to moderate amounts of dust from chloramine-T. Toward the end of this period, three years ago, she noticed more and more that exposure to this dust caused sneezing and coughing. Finally, these symptoms became so severe that she was transferred to another section of the factory. In this new location, she worked in a small closed room, ventilated only by filtered air brought in through a duct from the roof. This room was devoted entirely to filling sterile glass cartridges with a solution of procaine hydrochloride for dental use. No particular symptoms were noted for about two and one-half years in this occupation, but about that time the manufacture of halazone had greatly increased in volume, and dust from various operations involved was being discharged through ducts to the outside air at various locations. In September, 1943, the patient had a slight attack of dyspnea and was seen in the plant dispensary. She stated at the time that she might have been exposed to a small amount of chloramine-T, but could not be sure. She was given a capsule containing ephedrine, glucophylline, and neonal, and made no further complaint. In January, 1944, the patient came to the plant dispensary in great distress, gasping for breath. Typical asthmatic râles were present in the chest. The attack had occurred without warning while the patient was doing her usual work; she had been unaware of any odor of chloramine-T or halazone. Quick relief was secured by the administration of oxygen and 0.5 ml. of epinephrine. She returned to her former work, and suffered no further attacks until more than a month later when another, somewhat milder attack occurred under identical circumstances. It was not possible to show that any halazone dust gained access to the procaine room, but the air inlet for this room was located on the same roof as the exhaust from another department where halazone tablets were manufactured. Physical examination on Feb. 29, 1944, revealed a normally developed woman of rather small stature. The blood pressure was 108/70. All other physical findings were essentially normal; no abnormal sounds were heard in the chest.

CASE 6.—H. S., a married white man, 30 years of age, previously employed as a salesman, began work in the capsule-filling department of the pharmaceutical factory four years ago. The only case of allergy in the patient's entire family was one uncle who had hay fever. The patient had never had infantile eczema, hay fever, asthma, or urticaria before being employed. Pre-employment physical examination revealed a normally developed white man showing no abnormalities except a blood pressure of 130/90, moderate caries of the teeth, injected pharynx, small varicose veins in the legs, and flat feet. A roentgenogram of the chest revealed no evidence of infiltration, consolidation, or other active disease in either lung. The pleura over the right apex was slightly thickened, and the hilar shadows were slightly accentuated. There was no abnormality of the diaphragm, heart, aorta, or bony framework. He worked filling various types of capsules with powdered drugs for six months without any symptoms, but then began to notice that whenever he handled nembutal capsules, he would sneeze and suffer a sense of choking. He obtained an efficient dust-filter mask and wore it continuously while working for two months, but the symptoms continued. About that time he noticed that accidental exposure to the dust of chloramine-T, being handled by other workmen, produced the same symptoms. He suffered from a chronic cough, which was not relieved by medication. In September, 1941, he reported that these symptoms had been present for six weeks, and that they had been relieved by ephedrine and nembutal capsules and by an injection of epinephrine. At that time he was using three pillows in order

to sleep at night. Examination revealed the presence of dyspnea, but no abnormal breath sounds were heard. There was a loud, brassy cough. Two days after this examination, the patient reported with severe dyspnea, not provoked by any special exposure as far as he was aware. Typical asthmatic râles were present in the chest. The symptoms were relieved within ten minutes after an injection of 0.5 ml. of epinephrine. He was transferred to the shipping room, and did not complain of any symptoms at the plant dispensary, though he continued under the care of a private physician who treated him with ephedrine more or less continuously. He was tested by this physician for skin-sensitivity, and states he gave positive reactions to a number of common foods. However, treatment with various elimination diets failed to improve his symptoms, and he finally left this physician's care. On Dec. 9, 1941, he had an asthmatic attack during the night, at home. On December 27, he noticed generalized itching of the skin, swelling of the eyelids and face, and the appearance of urticarial wheals over the body. This could not be traced to any definite cause, industrial or otherwise, but lasted about four days and required hospital care. Early in 1942, the patient, on his own initiative, began using a spray of 1:100 ephinephrine and found this controlled his dyspnea without producing the side reactions caused by ephedrine. He has continued to use this medication ever since, practically every night. He reported only one attack of asthma at the plant dispensary in 1942; this occurred on February 12. No further attacks were reported until May, 1943, although he continued to have slight dyspnea every night if he did not use the epinephrine spray. From that time to the present, he has continued much the same as before. During the past two years, there has been little connection between the appearance of symptoms and any particular exposure at work; the patient finds that any sort of dust causes discomfort, whether encountered at home or in the shipping room. Two years ago, a vacation in another state brought complete relief of his symptoms, but last year a visit to the same locality brought no relief at all.

DISCUSSION

The facts presented in this paper suggest several points of interest:

1. As an example of allergy in a chemical industry it should invite greater attention to such problems in other occupations. To some measure, of course, this problem has received consideration in the past. To be most useful, however, such studies should be made regularly and through the combined efforts of the plant physician, allergist, and industrial engineer.

2. The main point of this paper is the demonstration of a simple chemical substance of low molecular weight (211) which behaves, in a number of individuals, as a typical atopen. In support of this idea is the ability of this antigen to produce atopic symptoms and immediate whealing skin reactions to stimulate atopic reagin formation and to induce some evidences of desensitization. There have been some previous reports of hypersensitiveness to simple chemical substances, such as allergy to phthalic anhydride in a chemist, described by Kern,[2] and allergy to platinum compounds noted by Cohen.[3] Nevertheless, the concept generally prevails that simple chemical compounds are not complete atopens. The demonstration of the behavior of the sulfonechloramides as atopens in a fairly large group of individuals should broaden our point of view on this subject and should encourage us to look for other exceptions to the common concept.

3. The even more intriguing possibility that the chloramides may behave as complete antigens deserves consideration. The usual haptenic role of simple chemical substances, requiring conjugation with larger molecules to act as complete antigens, is well known. It is usually conceded that only in this way can such an antigen produce anaphylactic sensitization or act as a precipitinogen. A possible exception to this concept was revealed in the work of Landsteiner and Chase[3] on picryl chloride. In practically all of the previous experiments of other workers, the chemicals investigated lacked the power to produce the immediate whealing skin response, or the passive transfer reaction in man. Since the sulfonechloramides behave as complete atopens it may be possible that they

may also behave as complete antigens. It is hardly necessary to point out that if such simple chemicals can be definitely shown to constitute complete antigens, our immunologic concepts of antigens and hypersensitiveness will need modification. Experiments are now under way to produce the anaphylactic response in the guinea pig and precipitins in the rabbit.

4. The large numbers of allergic individuals in whom the specific allergen cannot be located leads us to believe that, in these cases, we may be dealing with allergens of obscure action or obscure identity. In the first group there may be chemical substances in food, air, etc., which are incapable of giving skin reactions. Their behavior would be similar to the action of aspirin, but, unlike aspirin, they are not labeled and therefore are unidentified. In the second group there may be chemical substances which are capable of giving skin reactions, but whose identity has not been disclosed. If the sulfonechlodamides can produce allergic symptoms and skin reactions, then perhaps there may be other, as yet unidentified, substances in the air, food, and water, of similarly simple structure, which are capable of acting in like manner. Perhaps the so-called nonspecific excitants in coal smoke, wood smoke, gasoline fumes, paints, perfumes, etc. are specific allergens after all. At any rate, the experience we have had with the sulfonechloramides should be a warning that such possibilities should not be disregarded.

SUMMARY

1. Asthma and rhinitis due specifically to the inhalation of dust of the water disinfectants, chloramine-T and halazone, are reported in fourteen workers exposed to these chemicals.

2. These simple chemical substances of low molecular weight have been shown to behave as true atopens, by producing immediate whealing skin reactions by direct test and by passive transfer.

3. The experiences cited suggest a number of possibilities: (a) that such simple chemicals may act as complete antigens; (b) that simple chemical allergens, as yet of unidentified nature, may be present in food, drink, and air; and (c) that chemical irritants, hitherto regarded as acting in a nonspecific manner, may, on re-examination, exhibit specific allergenic behavior.

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185 NORTH WABASH AVE.

REACTIONS TO ANTIPNEUMOCOCCAL RABBIT SERUM*†‡

The Role of Reversed Passive Anaphylaxis and of Inherent Toxicity of Antiserum

Failure of Heat to Separate Sensitizing From Therapeutic Antibody An Experimental and Clinical Study

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PROMPT untoward reactions to therapeutic injections of antipneumococcal serum are common. Reactions vary in incidence and severity. Death follows about one in five hundred injections of serum.[1] Rutstein, Reed, Langmuir, and Rogers[2] reviewed the literature and made a comprehensive clinical study of this problem. They classified and discussed the reactions under the headings thermal, anaphylactic, circulatory, and miscellaneous. In patients who had anaphylactic reactions they reported a history of allergy in only 15 per cent and positive cutaneous reactions in only 20 per cent. Anaphylactic reactions can be expected in patients with positive allergic reactions to the serum, but no explanation has been offered for the anaphylactoid reactions that occur in patients with negative skin reactions.

This study was begun with the idea that the phenomenon of reversed passive anaphylaxis[3] would explain the anaphylactic reactions that follow antipneumococcal serum injections in patients who had negative cutaneous, conjunctival, and intravenous reactions to the serum. Experiments on guinea pigs and rabbits and a tabulation of some antipneumococcal serum reactions in patients are presented to support this idea. In reversed passive anaphylaxis the subject is sensitized by the presence of antigen and is shocked, after an interval, by immune serum—a reversal of the sequence in conventional passive anaphylaxis. During the experiments, one batch of serum was found to be highly toxic for guinea pigs. The possible role of toxic serum in the circulatory type of reaction is discussed. Reported, too, are unsuccessful attempts to separate the sensitizing or anaphylactic antibody from the therapeutic antibody by heating the serum. This attempt was suggested by Loveless'[4] separation of reagin from human inhibiting or thermostable antibody by heating the serum to 56° C. for five hours. Thermal reactions hitherto studied[5, 6] will not be discussed here.

EXPERIMENTAL DATA

Solutions of Types I and II pneumococcal polysaccharides were used as antigen and several different batches of Types I and II antipneumococcal rabbit serum were used as antibody in all of the anaphylactic experiments. The exact weight-by-volume strength of the polysaccharides used in the guinea pig experiments is not known. However, they gave positive interfacial precipitative re-

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actions in dilutions of 1:4,096 when stratified on 1:5 dilutions of their type-specific antisera; 1:10 dilutions of the polysaccharides in saline had a precipitin titer (antigen-dilution) of 1:512. The concentrated polysaccharide solutions used in the rabbit experiments were from a different source. They contained 10 mg. per milliliter. A solution containing 1 mg. per milliliter had the same precipitin titer, 1:4,096, as the concentrated solutions used in the guinea pig experiments.

Experiment 1.—Experiment 1 was done to show that the antigen and antibody could produce conventional passive-anaphylactic death and to determine the effective sensitizing and shocking doses.

EXPERIMENT 1. CONVENTIONAL PASSIVE ANAPHYLAXIS; ANTIPNEUMOCOCCAL RABBIT SERUM AS SENSITIZING ANTIBODY; PNEUMOCOCCAL POLYSACCHARIDE AS SHOCKING ANTIGEN

GP	TYPE I ANTISERUM I. A. (ML.)	REACTION	INTERVAL (HR.)	1:10 TYPE I POLYSACC. I. V. (ML.)	REACTION
		Group A. Sensitizing doses of antiserum varied			
1	0.1	0	48	0.6	Immediate death
2	0.2	0	48	0.6	Immediate death
3	0.4	0	48	0.5	Immediate death
4	0.8	0	48	1.5	Immediate death
5	1.6	0	48	0.6	Immediate death
6	3.2	0	48	1.2	Convulsions Recovered
		Group B. Sensitizing doses of antiserum constant			
1	0.2	0	48	0.4	Immediate death
2	0.2	0	48	0.6	Immediate death
3	0.2	0	48	0.7	Immediate death
4	0.2	0	48	0.7	Immediate death
5	0.2	0	48	0.6	Immediate death

GP = Guinea pig.
Polysacc. = Polysaccharide.
I. A. = Intra-abdominal injection.
I. V. = Intravenous injection.
Shocking doses of polysaccharide were continued until dyspnea began.
All reactions were typical of anaphylaxis.

EXPERIMENT 2. SPECIFICITY OF ANAPHYLACTIC REACTIONS

GP	TYPE II SERUM I. A. (ML.)	REACTION	INTERVAL (HR.)	HETEROLOGOUS POLYSACC. TYPE I I. V. (ML.)	REACTION	INTERVAL (MIN.)	HOMOLOGOUS POLYSACC. TYPE II I. V. (ML.)	REACTION
				Group A				
1	0.2	0	16	0.8	0	15	1.0	Immediate death
2	0.2	0	16	0.8	0	15	1.0	Immediate death
3	0.2	0	16	0.8	0	15	1.0	Immediate death
4	0.2	0	16	0.8	0	15	1.0	Convulsion Recovered slowly
	TYPE I			TYPE II			TYPE I	
				Group B				
1	0.2	0	16	0.8	0	15	1.0	Immediate death
2	0.2	0	16	0.8	0	15	1.0	Immediate death
3	0.2	0	16	0.8	0	15	1.0	Immediate death
4	0.2	0	16	0.8	Convulsion Recovered promptly	15	1.0	Immediate death

All reactions were typical of anaphylaxis.

EXPERIMENT 3. REVERSED PASSIVE ANAPHYLAXIS
(Intra-Abdominal Sensitization)

	ANTIGEN I. A.			ANTIBODY I. V.	
GP	TYPE I POLYSACC. 1:10 (ML.)	REACTION	INTERVAL (HR.)	TYPE I ANTIPNEUMO. SERUM (ML.)	REACTION
			Group A		
1	5.0	0	96	2.0	Mod. dyspnea†
2	5.0	0	96	3.0	Mod. dyspnea†
3	5.0	0	96	3.0	Slt. dyspnea
4	5.0	0	96	3.0	Mkd. dyspnea Convulsion*
	TYPE I POLYSACC. CONC.			TYPE I ANTIPNEUMO. SERUM	
			Group B		
1	1.0	0	4	2.0	Mod. dyspnea
2	1.0	0	4	2.0	Mkd. dyspnea
3	1.5	0	4	2.0	Mod. dyspnea
4	1.5	0	4	2.0	Mkd. dyspnea
5	2.0	0	4	2.0	0
	TYPE II POLYSACC. CONC.			TYPE II ANTIPNEUMO. SERUM	
			Group C		
1	0.1	0	24	2.0	0
2	0.5	0	24	2.0	Mod. dyspnea
3	1.0	0	24	2.0	Mod. dyspnea Convulsions*
	TYPE II POLYSACC. 1:100			TYPE II ANTIPNEUMO. SERUM	
			Group D		
1	0.2	0	24	2.0	0
2	0.4	0	24	2.0	0
3	0.8	0	24	2.0	0
	TYPE II POLYSACC. 1:10			TYPE II ANTIPNEUMO. SERUM	
			Group E		
1	0.2	0	24	2.0	0
2	0.4	0	24	2.0	0
3	0.5	0	4	1.5	Mod. dyspnea†
4	0.5	0	4	1.5	0
5	0.5	0	4	3.0	Mod. dyspnea†
6	0.5	0	4	2.0	0
7	0.5	0	4	3.0	Mod. dyspnea
	TYPE II POLYSACC. 1:10			TYPE II ANTIPNEUMO. SERUM	
			Group F		
1	3 & 2‡	0	24	1.0	Slt. dyspnea†
2	3 & 2	0	24	1.0	0
3	3 & 2	0	24	1.25	0
4	3 & 2	0	24	1.0	0
5	3 & 2	0	24	2.0	Slt. dyspnea†
6	3 & 2	0	24	2.0	Slt. dyspnea
7	0.2 & 0.1	0	24	1.0	Mkd. dyspnea†
8	0.2 & 0.1	0	24	1.0	Slt. dyspnea†

Slt. = Slight. Mod. = Moderate. Mkd. = Marked.
Dyspnea was chiefly expiratory.
Type I serum = Lot No. A-305.2.
Type II serum = Lot No. A-387.1.
Antipneumo. Serum = Antipneumococcal rabbit serum.
Polysacc. Conc. = Concentrated polysaccharide.
See Experiments 4 and 6 for negative controls.
*Died during the night.

†Onset of reaction ten to twenty minutes after completion of shocking injection of antiserum.

‡Two I. V. sensitizing injections given at thirty and at eight hours before the shocking doses.

Experiment 2.—Experiment 2 shows that the anaphylactic reactions were type-specific. Animal 4, Group B, recovered promptly from the reaction to the injection of Type II serum. It is assumed that this was not a specific reaction because typical anaphylactic death occurred fifteen minutes later when Type I serum was given.

Experiment 3.—Experiment 3 shows that reversed passive anaphylaxis can be produced, inconstantly, by intra-abdominal sensitizing injections of polysaccharide, followed by intravenous shocking injections of the type-specific antiserum. The volume and concentration of polysaccharide, the interval between sensitizing and shocking doses, and the amount of antiserum were varied. Eighteen of thirty-two guinea pigs had reversed passive-anaphylactic reactions. Two died. Three other animals had marked, nine had moderate, and four had slight, dyspnea. Seven of the reactions were delayed; they began ten to twenty minutes after the shocking injection of serum. The more severe and more frequent reactions occurred in Group B in which concentrated polysaccharide preceded the shocking dose of antibody by only four hours.

Experiment 4.—Experiment 4 shows that reversed passive anaphylaxis can be produced, quite regularly, by intravenous sensitizing injections of polysaccharide followed in about an hour by intravenous shocking injections of type-specific antiserum. Note the shorter intervals between sensitizing and shocking doses, the variations in the amount and concentration of the polysaccharide, and the variations in the amount of antiserum. Nine of the seventeen animals had marked, six had moderate, and one had slight dyspnea promptly. Only one failed to react. Twelve died during the night. None of the controls reacted.

EXPERIMENT 4. REVERSED PASSIVE ANAPHYLAXIS
(Intravenous Sensitization)

	ANTIGEN I. V.			ANTIBODY I. V.	
GP	TYPE II POLYSACC. CONC. (ML.)	REACTION	INTERVAL (MIN.)	TYPE II ANTIPNEUMO. SERUM LOT A387.1 (ML.)	REACTION
			Group A		
1	0.5	0	60	2.0	Mod. dyspnea*
2	1.0	0	60	2.0	Mod. dyspnea*
3	1.0	0	60	2.5	Mkd. dyspnea*
4	1.0	0	60	1.5	Mkd. dyspnea*
	TYPE I POLYSACC. CONC.			TYPE I ANTIPNEUMO. SERUM LOT A305.2	
			Group B		
1	1.0	0	80	2.0	Mod. dyspnea*
2	1.0	0	80	2.0	Mod. dyspnea*
3	0.5	0	80	2.0	Mkd. dyspnea*
4	1.0	0	80	2.0	Mkd. dyspnea
5	1.0	0	80	2.0	Mkd. dyspnea
	TYPE II POLYSACC. 1:10			TYPE II ANTIPNEUMO. SERUM LOT A387.1	
			Group C		
1	1.0	0	60	2.0	Slt. dyspnea*
2	1.0	0	60	2.0	Mkd. dyspnea*
3	0.5	0	60	1.0	Mkd. dyspnea
4	0.5	0	60	1.0	Mkd. dyspnea*
5	0.5	0	60	1.0	Mod. dyspnea*
6	0.5	0	60	1.0	0

EXPERIMENT 4—CONT'D *

	ANTIGEN I. V.		ANTIBODY I. V.		
	TYPE I POLYSACC. 1:10			TYPE I ANTIPNEUMO. SERUM LOT A305.2	
			Group D		
1	1.0	0	60	2.0	Mkd. dyspnea*
2	1.0	0	60	2.0	Mod. dyspnea
			CONTROLS		
	COCA'S SOLUTION		INTERVAL (HR.)	TYPE I ANTIPNEUMO. SERUM LOT A305.2	
			Group E		
1	1.0	0	1	2.0	0
2	1.0	0	1	2.0	0
3	1.0	0	1	2.0	0
	COCA'S SOLUTION			TYPE II ANTIPNEUMO. SERUM LOT A387.1	
			Group F		
1	1.0	0	1	2.0	0
2	1.0	0	1	2.0	0
3	1.0	0	1	2.0	0
4	1.0	0	1	1.0	0
5	1.0	0	1	1.0	0
6	1.0	0	1	1.0	0

All animals except 1,*A*, 1,*C*, and 6,*C*, and the controls were prostrated in addition to the dyspnea, which was chiefly expiratory.

*Died forty-five minutes or more after the shocking dose of antiserum.

Experiment 5.—Experiment 5 shows that reversed passive anaphylaxis was produced in five of eight rabbits. Four of six rabbits had severe reactions when given the shocking dose of antipneumococcal serum as much as four hours after the sensitizing injections of 25 to 35 mg. of type-specific polysaccharide. A fifth one had a milder reaction. Two of the three animals that did not react received the injections of polysaccharide and serum at an interval of one hour. The doses of serum were smaller, 7 and 8 milliliters. The other which did not react received a sensitizing dose of only 10 mg. of polysaccharide and a shocking dose of only 7 ml. of serum. All injections were given intravenously.

EXPERIMENT 5. REVERSED PASSIVE ANAPHYLAXIS IN RABBITS (Intravenous Sensitization)

RABBIT	I. V. POLYSACC. TYPE II (ML.)	REACTION	INTERVAL (HR.)	I. V. ANTIPNEUMO. SERUM TYPE II (ML.)	REACTION
			Group A		
1	1.0	0	4	10	Moderate*
2	2.5	0	4	10	Severe†
3	3.0	0	1	7	None
4	3.0	0	1	8	None
	TYPE I			TYPE I	
			Group B		
1	2.5	0	4	10	Severe†
2	3.0	0	4	10	Severe†
3	3.5	0	4	8	Severe†
4	1.0	0	4	7	None

1 ml. Polysacc. = 10 mg.

*Moderate = Dyspnea, ears awry, "sick."

†Severe = Nystagmus, sprawled, hind legs out, defecation, urination, neck limp, ears awry, severe dyspnea. Unexpected recovery.

TABLE I. REACTIONS TO ANTIPNEUMOCOCCAL RABBIT SERUM IN THIRTY-FIVE CASES OF PNEUMONIA

CASE	NUMBER OF SERUM INJECTIONS	NUMBER OF REACTIONS	TYPE OF REACTION
	Group A. Thirteen fatal cases		
1	1	1	Severe asthma and fever
2	2	2	One chill and fever One severe anaphylaxis thirty-six days after first injection
3	1	1	Dyspnea, pulmonary edema Convulsions, death
4	1	1	Sudden death within one hour
5	3	2	One chill and fever One urticaria with fever
6, 7, and 8	14	6	Chills and fever
9, 10, 11, 12, and 13	14	0	Moribund
	Group B. Twenty-two recovered cases		
1	1	1	Severe asthma, nearly fatal
2	3	1	Dyspnea, orthopnea, cyanosis Chill and fever
3	1	1	Orthopnea, dyspnea Chills and sweats
4	1	1	Cough and dyspnea Chill
5	1	1	Dyspnea Chills
6	1	1	Cough, flushing Fever
7	1	1	Shock in six hours
8	21	1	Chill and fever
9, 10, 11, and 12	9	4	Chills and fever
13-22	13	0	
Totals 35	88	25	

Cases 1,*A* and 1 to 6,*B* = Respiratory reversed passive anaphylaxis.
Case 5,*A* = Urticarial reversed passive anaphylaxis.
Case 2,*A* = Questionable reversed passive anaphylaxis. Tests for sensitivity were negative.
Cases 3,*A* and 7,*B* = Circulatory reactions.

The data in Table I were compiled from hospital records of thirty-five cases of pneumonia. These patients had received antipneumococcal serum. Descriptions of the reactions were made by house officers as routine progress notes. All of the reactions were observed before the theory was conceived that some reactions might be due to reversed passive anaphylaxis. Any interpretation of the mechanism of the reactions must, therefore, be tentative. With these reservations, it will be seen that seven of thirty-five patients had respiratory reactions, and one had an urticarial reaction which might be considered of the reversed passive-anaphylactic type. There was one questionable reversed passive-anaphylactic respiratory reaction in a patient who did not react to tests for sensitivity although he had had serum thirty-six days previously. One patient went into profound shock, and another had pulmonary edema after serum injections. These were thought to be circulatory reactions.[2] One patient died suddenly while the nurse was out of the room. Seventeen patients had chills and fever. Six of these also had respiratory symptoms. All of these patients had negative cutaneous, conjunctival, and intravenous reactions to rabbit serum. None of the thirteen deaths could be attributed with certainty to the serum. Cases 3 and 4, *A*, were debatable.

Experiment 6.—Experiment 6 shows that intravenous injections of Lot A373.1 Type I antipneumococcal rabbit serum produced fatal pulmonary edema regularly in guinea pigs. The reactions consisted of dyspnea and prostration

coming on five to fifteen minutes after the serum injection. They lasted ten to forty-five minutes. Bloody froth poured from the nose and mouth just before death. The respirations were rapid, deep, and labored but did not have as marked expiratory emphasis as the anaphylactic reactions.* Lots A305.2 (Experiment 4,*E*) and 273.3 of Type I and Lots A387.1 and A329.1 of Type II antiserum caused no reactions. The absence of pulmonary edema in the guinea pigs in Experiments 3 and 4 serves as additional negative controls for this experiment.

EXPERIMENT 6. INHERENT TOXICITY OF SOME ANTIPNEUMOCOCCAL RABBIT SERUM

GP	I. V. TYPE I SERUM LOT A373.1 (ML.)	REACTION
	Group A	
1	2.0	Prompt death, pulmonary edema
2	2.0	Prompt death, pulmonary edema
3	2.5	Prompt death, pulmonary edema
4	0.6	Prompt death, pulmonary edema
5	2.0	Prompt death, pulmonary edema
6	0.8	Prompt death, pulmonary edema
	Lot A273.3	
7	2.0	None
	TYPE II SERUM LOT A387.1 (ML.)	
	Group B	
1	2.25	None
2	2.75	None
	TYPE II LOT A329.1	
3	2.0	None

7,*A* and Group *B* are negative controls.
Groups *E* and *F*, Experiment 4, are additional negative controls for this experiment.

Experiment 7.—Experiment 7 shows that heating Types I and II antipneumococcal rabbit serum to 60° C., to 65° C., and to 70° C. for one to twenty-four hours did not destroy the capacity to produce fatal passive-anaphylactic sensitization. Heating to 75° C. for five hours did not entirely destroy the anaphylactic antibody, but heating to 80° C. did.

Concentrated serum heated to 60° C. was somewhat murky. A 1:5 dilution heated to 60° C. was almost normal in appearance. All other samples of serum were diluted 1:5 before heating. At 65° C. there was definite opalescence but no sediment. At 70° C. there was rather marked opalescence and a trace of sediment. At 75° C. and at 80° C. the diluted serums were opaque with a good deal

*Dr. *Sanford Hooker* suggested: "that in explanation of the primary toxicity of Lot A373.1 the Forssman antigen-antibody system should be considered. Certain pools of antipneumococcal rabbit sera might contain heterophilic antibody in high titer as a response to the Forssman-like antigen in pneumococci. Such sera have been shown to be toxic to animals, e.g., guinea pigs, that contain Forssman's antigen in their tissues. The human blood group substance A resembles Forssman's antigen, and it is conceivable that patients of Groups A and AB might react unfavorably to sera sufficiently rich in Forssman's antibody. This consideration would not apply in the case of equine antisera because the horse has Forssman's antigen in his tissues and will not produce antibody against it (in accordance with the principle *horror autotoxicus*)."

Reply: Dr. Hooker should know that I am grateful for this and for other suggestions. It was felt at the time of the discussion that the absence of reactions in the sensitizing serum injections in Experiment 2 and in the negative controls in Experiment 4 ruled out the Forssman explanation of the reactions. Later, however, four of five guinea pigs accepted, with no reaction, intravenous injections of 2+ ml. of Lot A373.1 serum to which ground guinea pig kidney (Forssman's antigen) had been added. This, plus the inability of Redfern[13] (whose report had been overlooked) to separate the toxicity from heterophile antibody indicate the need for more detailed consideration of Dr. Hooker's suggestion.

of sediment. The sediment was mixed with supernate by shaking, before injection into the animals. The precipitative titer of the 1:5 serum heated to 60° C. for five hours was reduced from 1:512 to 1:128.

EXPERIMENT 7. EFFECT OF HEAT ON SENSITIZING POWER OF ANTIPNEUMOCOCCAL RABBIT SERUM

	I. A. ANTIBODY			I. V. ANTIGEN	
GP	CONC. TYPE I 60° C. 1 HR. (ML.)	REACTION	INTERVAL (HR.)	TYPE I POLYSACC. 1:10 (ML.)	RESULT
			Group A		
1	0.2	0	48	1.0	Immediate anaphylactic death
2	0.2	0	48	0.6	Immediate anaphylactic death
3	0.2	0	48	0.6	Immediate anaphylactic death
4	0.2	0	48	0.4	Immediate anaphylactic death
5	0.2	0	48	0.6	Immediate anaphylactic death
6	0.2	0	48	0.6	Immediate anaphylactic death
	1:5 TYPE I 60° C. 24 HR.				
			Group B		
1	1.0	0	55	0.8	Immediate anaphylactic death
2	1.0	0	55	0.8	Immediate anaphylactic death
	1:5 TYPE II 65° C. 5 HR.			TYPE II POLYSACC. 1:10	
			Group C		
1	1.5	0	48	1.+	Immediate anaphylactic death
2	1.5	0	48	1.+	Immediate anaphylactic death
	1:5 TYPE II 70° C. 5 HR.			TYPE II POLYSACC. 1:10	
			Group D		
1	1.5	0	24	1.+	Immediate anaphylactic death
2	1.5	0	24	1.+	Immediate anaphylactic death
	1:5 TYPE I 75° C. 5 HR.			TYPE I POLYSACC. 1:10 I. V.	
			Group E		
1	1.5	0	24	1.+	Mod. dyspnea prostrated
2	1.5	0	24	1.+	None
	1:5 TYPE I 80° C. 5 HR.			TYPE I POLYSACC. 1:10 I. V.	
			Group F		
1	1.5	0	24	1.+	None
2	1.5	0	24	1.+	None

Conc. Type I 60° C. 1 hr. = Concentrated Type I antipneumococcal rabbit serum heated to 60° C. for one hour.

1:5 Type II 65° C. 5 hr. = 1 to 5 dilution of Type II serum in saline heated to 65° C. for five hours.

DISCUSSION

Experiments 1 and 2 confirm the findings of Avery and Tillett[7] and others that guinea pigs, passively sensitized by antipneumococcal rabbit serum, can be shocked by injections of type-specific polysaccharide. Experiments 1 and 2 also show that the antigen and antibody used were potent and type-specific.

Experiments 3, 4, and 5 show that reversed passive anaphylaxis can be produced in guinea pigs and in rabbits under circumstances immunologically comparable to, but not identical with, those for which serum is given to patients with pneumonia. Table I shows that a fairly large percentage of patients have what seems to be reversed passive-anaphylactic reactions to injections of antipneumococcal serum. The presumption is that the infecting organisms supply the necessary antigen. Bullowa, Bukantz, and de Gara[8] have shown that measurable excesses of polysaccharide do occur in pneumonia.

The reversed anaphylyactic reactions in the guinea pigs agreed with the descriptions of immediate and delayed fatal and nonfatal anaphylactic reactions by Dean, Williamson, and Taylor,[9] Williamson,[10] and others. In general, larger amounts of polysaccharide intravenously at shorter intervals, before shocking with antiserum, gave the more frequent and more severe reactions. More detailed studies now in progress will be needed to determine the optimal doses of antigen and antibody and the most effective interval between sensitizing and shocking doses. The reversed passive-anaphylactic reactions in the rabbits conformed closely to the descriptions of Opie and others[3] Further support of the clinical importance of the concept of reversed passive anaphylaxis as a cause of reactions to antipneumococcal rabbit serum comes from an analysis of Rutstein's[2] Table 12; Cases 7 and 24 are typical examples, while Cases 11, 15, 20, and perhaps 3 are probable examples of this phenomenon.

These clinical and experimental data seem to justify the tentative conclusion that: when cutaneous, conjunctival, and intravenous tests for rabbit serum sensitivity result negatively, anaphylactic reactions following injections of antipneumococcal rabbit serum are due to the phenomenon of reversed passive* anaphylaxis, in which the antigen is supplied by the infecting organism in vivo and the anaphylactic antibody is supplied by the injected antiserum. No attempt to explain these reactions has been found in the literature. There is certainly no evidence that the reactions are due to sensitivity to rabbit serum proteins.

The clinical significance of the toxic effects of the batch of serum studied in Experiment 6 is not clear. This serum has not been used on patients. However, there is good reason for the belief that some clinical circulatory reactions are due to a toxic effect inherent in isolated batches of antiserum. In support of this belief are: (1) the pulmonary edema in the guinea pigs in Experiment 6, in Patient 3 in Group A of Table I, and in several of Rutstein's[2] patients; (2) profound shock in Patient 7,B of Table I; (3) the reports of Dean, Williamson, and Taylor,[9] Bullowa,[1] and others who found batches of rabbit and horse antiserum which were toxic for guinea pigs and for man. Redfern[13] described pulmonary edema in guinea pigs from toxic antiserum. The toxicity was inseparable from

*Dr. *Stearns Bullen*, in discussing the paper, questioned the correctness of the term "passive."

Reply: It is a searching and an unanticipated question. The term passive has been retained, however, because there is no reason to think that the immune mechanism of the patient is actively involved in the anaphylactic reaction. In active anaphylaxis the anaphylactic antibody is produced by the animal or patient in response to the antigen. In patients with pneumonia, as in passive anaphylaxis, the anaphylactic antibody is produced by another animal, but the antigen is aspirated instead of injected.

heterophile antibody. Anaphylaxis, in which shock and widespread vascular damage are so characteristic, would seem sufficient to explain some of the other so-called circulatory reactions in man.

In Experiment 7 failure to destroy the anaphylactic antibody by heat, without affecting the therapeutic value of the antipneumococcal serum, was disappointing in that it did not offer a method for preventing reversed passive anaphylaxis. Loveless[4] and others have shown that ragweed reagin, a sensitizing antibody, can be destroyed by heating human serum to 56° C. for five hours without demonstrably affecting the titer of the protecting thermostable antibody.

Reduced frequency and severity of reactions to antiserum is desirable. To this end, prompted by the data presented, the following procedures are suggested as worthy of clinical evaluation: First, that all batches of antipneumococcal rabbit serum be tested for toxicity by intravenous injections of 2.5 ml. into several guinea pigs before being released for clinical use. This should be done, in addition to current tests for chill- and fever-producing substances, at least until it can be shown that the sera which are toxic for guinea pigs are not toxic for human beings. Second, that cutaneous and conjunctival tests for sensitivity be done with immune serum instead of normal serum. If reactions to immune serum are positive, additional tests with normal serum should show whether the anticipated clinical reaction would be due to the animal protein or to the anaphylactic antibody.* Simultaneous tests with immune and with normal serum might be preferable. Wright and Hopkins[11] have shown that positive reactions can be produced in man by intracutaneous injections of antibody in the presence of antigen. Theoretically, antipneumococcal serum would give a positive cutaneous or conjunctival reaction in the presence of sufficient local pneumococcal antigen. But a negative reaction would not rule out the possibility of a local reversed passive-anaphylactic reaction in the lungs. It must be remembered that skin test reactions are generally conceded to be irregular and unreliable in human beings.

Third, if cutaneous and conjunctival tests are negative, a second intravenous test dose of perhaps 3 ml. might follow the conventional 1 ml. test dose before therapeutic antiserum is started.

More detailed animal and clinical studies are needed to permit the formulation of rules which will prevent reactions from antiserum given to patients who have homologous antigen in their tissues. Goodner and Horsfall,[12] who studied the effects of varying the doses of antigen on anaphylactic shock in animals passively sensitized by constant amounts of antiserum, have made a valuable beginning.

It is probable that the phenomenon of reversed passive anaphylaxis outlined here will explain similar reactions to other kinds of immune serum.

SUMMARY

1. Clinical and experimental evidence is presented to support the theory that, when cutaneous, conjunctival, and intravenous tests for rabbit-sensitivity are negative, anaphylactic reactions following injections of antipneumococcal rabbit serum are due to the phenomenon of reversed passive anaphylaxis, in which the antigen is supplied by the infecting organism in vivo, and the anaphylactic antibody is supplied by the injected antiserum.

*_Dr. Leo Criep_ pointed out appropriately that positive cutaneous reactions are to be expected when patients with pneumonia are tested with their type-specific antiserum. Such reactions would be manifestations of the E-E phenomenon described by Foshay in tularemia (J. Allergy 6: 360, 1935, and J. Infect. Dis. 59: 330, 1936).

Reply: A positive E-E reaction would indicate that pneumococcal antigen was present in the skin and would, therefore, suggest the possibility of an anaphylactic reaction to antipneumococcal serum.

2. Experimental evidence is presented which suggests that some, at least, of the circulatory reactions to antipneumococcal rabbit serum are due to toxicity inherent in certain batches of serum.

3. Efforts to destroy the anaphylactic antibody by heat without affecting the therapeutic titer of the antipneumococcal rabbit serum were unsuccessful. This is in sharp contrast to the ready destruction of human reagin by 56° C. in five hours.

4. The suggestions are made, subject to clinical evaluation, that the number and severity of circulatory and reversed passive-anaphylactic reactions to antipneumococcal rabbit serum might be lessened by (1) intravenous tests for toxicity on guinea pigs before releasing serum for clinical use, (2) the uniform use of immune serum, instead of or in conjunction with, normal serum, for cutaneous, conjunctival, and intravenous tests for sensitivity, and (3) a second intravenous test dose of perhaps 3 ml. of immune serum.

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Original Articles

THE ELECTROLYTE EXCRETION WITH VARIOUS FORMS OF THERAPY IN BRONCHIAL ASTHMA*†

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Stoesser and Cook[1] found that children with intractable asthma experienced notable clinical benefit from artificial fever therapy, ingestion of potassium chloride, or low sodium chloride diet. Striking improvement was also produced by these investigators[2] with the administration of pitressin (posterior pituitary antidiuretic principle), which causes retention of body water without addition of salt, followed by diuresis. It was assumed that the depletion of body sodium, whether by induced hyperpyrexia, potassium chloride diuresis, low salt intake, or pitressin, was the basis for relief of asthmatic symptoms. This assumption was supported by the observation that, in asthmatic patients given high sodium chloride diets, the increased salt intake promptly caused a return of asthma, but no determinations of mineral output were made.

In the present study, which includes two boys, 9 and 12 years of age, and four girls, 10, 12, 16, and 17 years of age, with chronic asthma, the children were placed on the pediatric metabolism ward and were subjected to various forms of therapy. During most of the observation periods, they were maintained on very low salt diet, carefully weighed and containing adequate caloric and dietary constituents with vitamin supplements. Diet and fluid intake were always measured, and the output of urine was analyzed for sodium, potassium and chlorine by the methods of Butler and Tuthill,[3] Shohl and Bennett,[4] and Harvey,[5] respectively. Stools were likewise analyzed in Cases 3, 4, 5, and 6. Other electrolytes, also determined, are not reported in this preliminary communication.

The 12-year-old boy (Case 1, H. B.) was studied for forty-four days, on a daily dietary intake of 120 mg. of sodium, 330 mg. of potassium, and 180 mg. of chlorine. There were two periods of potassium chloride administration. In the first, of five days' duration, he received from 3 to 12 Gm. daily, and in the second period, which lasted four days, from 2 to 8 Gm. extra of potassium chloride. During the six-day period of sodium chloride administration, the patient ingested an additional 1 to 8 Gm. of sodium chloride daily.

The 10-year-old girl (Case 2, M. M.) was under observation for eighty-four days. Her diet was similar to that of the first patient. There were two periods of potassium chloride therapy, during which the patient received from 2 to 5 Gm. daily in the first period which lasted four days, and from 2 to 10 Gm. in the second period, of eight days' duration. Pitressin was administered hypodermically for twenty-four to thirty-six hours on two occasions. The dose

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ranged from 0.2 to 0.5 c.c. every three hours. This child was given large amounts of sodium chloride (20 to 28 Gm. daily) for a period of six days.

The oldest girl (Case 3, V. H.) was on the metabolic ward for seventy-eight days. Her daily intake was as follows: 184 mg. of sodium, 477 mg. of potassium, and 264 mg. of chlorine. She received three treatments with pitressin. Sodium chloride (1 to 10 Gm. daily) was given for one eight-day period when the patient was also on an increased diet containing 1.458 Gm. of sodium, 1.211 Gm. of potassium, and 2.5 Gm. of chlorine. Adrenal cortex extract (Wilson) and the single adrenal cortical factor represented by desoxycorticosterone acetate (Cortate, Schering) were administered separately for five-day periods, the former in doses of 8 c.c. daily and the latter in doses of 8 to 20 mg. daily.

The daily intake in Cases 4, 5, and 6 was similar to that in Case 3. The 16-year-old girl (Case 4, M. H.) was under study for one hundred and twenty-three days. During a severe asthmatic attack she was placed on potassium chloride therapy for a period of seven days; she received 4 to 12 Gm. daily. Treatment with pitressin was instituted every three hours for a thirty-six-hour period on each of two different occasions; the dose varied from 0.2 to 0.5 cubic centimeters. The administration of adrenal cortex extract and subsequently of the single adrenal cortical factor (Cortate) was carried out in the identical manner as in Case 3.

Case 5 (S. H.), a girl 12 years of age, was under observation for forty-three days. She received desoxycorticosterone acetate in doses of 8 to 20 mg. daily throughout six days. Later, during a five-day period, adrenal cortex extract was administered in doses of 8 c.c. daily.

The 9-year-old boy (Case 6, W. H.) was on the metabolic ward for forty-two days. He was likewise given Cortate, and then adrenal cortex extract according to the same regimen. In addition, the patient was studied during a period of seven days in which both adrenal cortex extract and sodium chloride were given, the former in doses of 8 c.c. and the latter in doses of 1.6 to 4 Gm. daily. The results are summarized in Tables I and II.

Tables I and II reveal average daily excretion in milligrams of sodium, potassium, and chlorine with urine and stool determinations combined in Cases 3, 4, 5, and 6, and with urine only in Cases 1 and 2. A control period with

TABLE I. AVERAGE DAILY EXCRETION IN MILLIGRAMS OF SODIUM, POTASSIUM, AND CHLORINE (URINE ONLY)

CASE	CONTROL PERIOD EXCRETION			PERIODS*	KCl			PITRESSIN			NaCl		
	Na	K	Cl		Na	K	Cl	Na	K	Cl	Na	K	Cl
1. H. B.	143	388	157	A	165	3,159	2,760				579	160	1,573
12 yr.				B	54	455	345				789	191	1,358
				C	78	278	374				250	185	477
				A	306	673	871						
				B	226	1,649	1,891						
				C	39	962	692						
2. M. M.	134	278	376	A	634	1,047	1,584	313	270	526	3,060	415	11,337
10 yr.				B	42	73	124	448	291	251	2,614	275	4,235
				C	-	-	-	65	65	82	614	112	1,444
				A	120	2,134	2,051	216	431	196			
				B	919	1,639	3,581	311	153	309			
				C	68	376	318	87	149	49			

Daily dietary intake: Na, 120 mg.; K, 330 mg.; Cl, 180 mg.
*A = Period of treatment.
B = Day after therapy as discontinued.
C = Period of recovery.

TABLE II. AVERAGE DAILY EXCRETION IN MILLIGRAMS OF SODIUM, POTASSIUM, AND CHLORINE (URINE AND STOOL)

CASE	CONTROL PERIOD EXCRETION*			PERIODS*	KCl			PITRESSIN			NaCl			ADRENAL CORTEX EXTRACT			DESOXYCORTICO-STERONE ACETATE			NaCl AND ADRENAL CORTEX EXTRACT		
	Na	K	Cl		Na	K	Cl	Na	K	Cl	Na	K	Cl	Na	K	Cl	Na	K	Cl	Na	K	Cl
3. V. H. 17 yr.	58	336	274	A	496	4,325	4,090	62	197	414	3,091	439	4,718†	33	409	299	17	379	327			
				B	26	2,033	353	134	236	701	1,626	992	4,357†	25	369	168	112	357	302			
				C	12	872	409	77	237	319	422	611	874†	44	414	242	103	420	360			
				A				113	714	264												
				B				269	455	968												
				C				101	330	292												
				A				119	671	326												
				B				80	304	497												
				C				53	229	228												
4. M. H. 16 yr.	68	347	416	A	299	3,531	3,427	198	183	314				23	299	306	38	453	242			
				B	48	1,810	1,260	200	159	340				-	-	-	46	289	366			
				C	38	617	431	81	117	192				-	-	-	61	274	399			
				A				116	149	203												
				B				135	89	212												
				C				33	146	220												
5. S. H. 12 yr.	87	353	244	A										31	581	302	19	891	73			
				B										71	463	229	27	423	58			
				C										55	667	236	24	464	84			
6. W. H. 9 yr.	50	259	320	A										25	347	213	17	501	67	540	824	1,608
				B										63	472	261	31	404	271	720	507	1,472
				C										58	521	258	39	418	318	498	557	1,122

Daily dietary intake: Na, 174 mg.; K, 477 mg.; and Cl, 264 mg.

*A = Period of treatment.
B = Day after therapy was discontinued.
C = Period of recovery.

†Diet increased to contain: Na, 1.458 Gm.; K, 1.211 Gm.; and Cl, 2.5 Gm.

daily excretion for each patient is shown in the first column. In the other columns, results are listed in groups giving average daily excretion during the periods of treatment, excretion on the day after therapy had been stopped and that during the recovery phase. The latter varied from two to twelve days after potassium chloride therapy, two to twelve days following administration of pitressin, three to six days after ingestion of sodium chloride, five to seven days after use of adrenal cortex extract, and four to six days after desoxycorticosterone acetate.

The administration of potassium chloride caused large quantities of potassium and chlorine to be excreted. Sodium was also washed out with these ions until the excretion of sodium became very low. The patients showed some clinical improvement during potassium chloride therapy. The pitressin treatment was associated with an excretion of moderate amounts of sodium, potassium, and chlorine. There was marked relief from asthmatic symptoms. From previous physiologic studies on pitressin[6-8] it had been assumed that these electrolytes were retained during the antidiuretic phase, and that large quantities were lost from the body in the diuresis immediately following. Therefore, it was most interesting that the mineral studies revealed a lack of consistency in the excretion of sodium and chlorine in spite of the uniform clinical improvement in asthma noted after pitressin therapy. Possibly other factors than the loss of sodium play a role in producing the beneficial effect.

The ingestion of sodium chloride in considerable quantities swept out a significant amount of potassium. While Case 2 (M. M.) was ingesting 20 to 28 Gm. of sodium chloride daily, much smaller amounts of sodium and chlorine were excreted. During this period she apparently retained a large amount of water and sodium chloride, as evidenced by her marked weight increase from 20.376 to 22.167 kilograms. In all the patients, the asthma became more severe following increased intake of sodium chloride. Adrenal cortex extract produced a retention of sodium but permitted the excretion of potassium. This effect was accentuated by administration of Cortate. In the 9-year-old boy (Case 6, W. H.), who had the mildest asthmatic symptoms, there was little effect from administration of adrenal cortex extract or of desoxycorticosterone. When sodium chloride was added to the adrenal cortex extract, however, his symptoms of asthma became much more severe.

SUMMARY

1. In selected cases of chronic asthma in children, the ingestion of potassium chloride lead to a diuresis which did cause a loss of sodium from the body.

2. In the majority of the periods of observation, this situation was associated with an apparent improvement in the severity of the asthmatic symptoms.

3. On the other hand, the disease was aggravated by the retention of sodium and the excretion of potassium which occurred with the ingestion of sodium chloride and the administration of adrenal cortex extract and desoxycorticosterone acetate.

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SPUTUM CHOLESTEROL IN BRONCHIAL ASTHMA*

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THAT cholesterol is one of the components of sputum has long been established.[1, 2] The first extensive study of this subject was made by Kelly and Pinner[3] in 1928. They examined the sputa from patients with active pulmonary tuberculosis, bronchiectasis, and pneumonoconiosis. They found that the cholesterol content per gram of dried sputum ranged from an average of 8.75 mg. in patients suffering from active tuberculosis with cavitation to 4.67 mg. in patients with fibrotic pulmonary tuberculosis. They concluded that the cholesterol content of the sputum "has a definite though not a constant relation to the type of pulmonary lesion."

Recently, Bruger and Rosenblatt[4] analyzed the sputum of fifty patients with various pulmonary diseases. They observed that all forms of suppurative bronchopulmonary diseases were accompanied by high sputum cholesterols. In contrast, patients with nonsuppurative diseases (two with silicosis, two with bronchial asthma, and two with congestive heart failure) were associated with little or no sputum cholesterol.

Bronchial asthma is associated with expectoration of varying amounts of tenacious sputum. The onset and course of a paroxysm is seldom productive, but the end of the attack is ushered in by the expectoration of measurable amounts of sputum. The amount of sputum raised depends upon the type and stage of asthma and the nature and extent of the disease. Sputum is raised principally through the reflex action of cough, by the constant wavelike action of the ciliated epithelial cells, and by gravity through posture.

It has been suggested that the cholesterol content of sputum is an index of the degree of bronchopulmonary destruction.[4] Therefore, it was considered of interest to determine the cholesterol content of the sputum of asthmatic patients for the purpose of evaluating the diagnostic and prognostic importance of such determinations. No such study had previously been made on a large group of asthmatic patients.

The cholesterol content of the sputum was determined on fifty-one adult patients suffering from symptoms of bronchial asthma only. Cholesterol determinations were repeated on the sputa of seventeen patients after an interval of from four to six months.

Results were correlated with all available clinical information that could be obtained from the history, physical examination, skin tests, and laboratory procedures including x-rays of the lungs and sinuses. After the cholesterol

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determinations were completed the cases were arranged in order of increasing amounts of cholesterol (Table I) to determine whether there was any correlation between the amount of cholesterol in the sputum and the clinical findings.

METHOD FOR THE DETERMINATION OF CHOLESTEROL IN SPUTUM

The sputa were collected as twenty-four-hour specimens in bottles containing tricresol to prevent bacterial growth. The patients were instructed to stop all medication during this period and to avoid contamination of the sputa as far as possible with saliva or nasal secretions.

Cholesterol was determined by a modification of Bloor's method.[5] Bruger and Rosenblatt used a 3 per cent aqueous solution of sodium hydroxide to hydrolyze a portion of the sputum specimen. Since it is very difficult to obtain a homogeneous sampling of sputum due to the large clumps and heavy mucus a more accurate sampling was obtained by hydrolyzing the entire twenty-four-hour sputum specimens with an equal volume of 3 per cent sodium hydroxide solution, and the cholesterol was determined on aliquots of this clear sputum digest. Care was taken to check the volume after hydrolysis and replace any water lost through evaporation. Two milliliters of the sputum digest were put into a 15 ml. centrifuge tube containing 12 ml. of 3:1 alcohol-ether mixture. The tube was stoppered and its contents mixed and allowed to stand overnight to insure complete extraction. The tubes were then centrifuged and the clear supernatant fluid was poured off into a 100 ml. capacity beaker. This alcohol-ether extract was evaporated to dryness in an incubator set at 60° C. The residue in the beaker was extracted with three washings of 3 ml. of chloroform each. The beaker containing the 3 ml. washings of chloroform was placed in an incubator set at 45° to 50° C. and allowed to evaporate to approximately 1 milliliter. In order to extract all of the cholesterol from this residue extractions with warm chloroform were necessary. The chloroform extractions were filtered into a 10 ml. graduated glass-stoppered cylinder. The volume was made up to 4 ml. with chloroform, and if this volume had been exceeded by the washings the cylinder was placed in the incubator for further evaporation. To each sample was added 1 ml. of a standard containing 0.1 mg. of cholesterol per milliliter, bringing the total volume up to 5 milliliters. By addition of this small amount of cholesterol to each sample more accurate colorimetric readings could be obtained. The standard solution used for comparison contained 0.4 mg. of cholesterol in 5 ml. of chloroform. This standard solution and the unknowns were prepared simultaneously with 2 ml. of acetic anhydride and 0.1 ml. of concentrated sulfuric acid. Calculations were made in the usual manner, and the standard amount of cholesterol which was added to each sample was subtracted from the final result.

RESULTS

The cholesterol in the sputa of fifty-one patients ranged from 7 to 55 mg. per cent. The volume of sputum per twenty-four hours does not seem to influence the concentration of cholesterol per milliliter. Table I shows that some of the larger volume twenty-four-hour sputum samples give high values for cholesterol per milliliter, whereas others give low values. This is also the case in some of the smaller volume twenty-four-hour sputum samples. There is no relation between the duration of the asthmatic symptoms and the amount of sputum cholesterol. X-ray interpretation of the lungs seldom paralleled the results obtained on sputum cholesterols. No lipiodol bronchograms were made. The majority of the films showed slight or moderate root branch or hilar thickening. However, when there was definite evidence of bronchiectasis the sputum cholesterol was increased (Cases 34, 35, 36, 45, 47, 48, and 49, Table I).

The sputa from the patients of the skin-negative, infective group contain more cholesterol than those from the skin-sensitive group where the specific causes are pollens, inhalants, and foods. The majority of the infective group showed sputum cholesterols ranging from about 25 to 55 mg. per cent, but in three patients of this group the figures were comparatively low, 13, 16, and 17 mg. per cent (Cases 6, 10, and 15, Table I).

The majority of the patients in the skin-sensitive group showed a sputum cholesterol ranging from 7 to about 25 mg. per cent. The two of this group

TABLE I

NUMBER	CASE	SPUTUM VOLUME IN 24 HR. (ML.)	CHOLESTEROL IN SPUTUM		ALLERGIC CRITERIA	X-RAY OF LUNGS	X-RAY OF SINUSES	NATURE OF ASTHMA
			MG. PER CENT	MG. 24 HR.				
1	S. S.	20	7	1.4	I,* II,† III‡	Moderate root branch thickening	Slight membranous infiltration of antra and ethmoids	Slight asthma following hay fever season and occasionally during winter months
2	L. S.	17	9	1.5	I, II	Slight old central thickening	Negative	Mild asthma during and following fall hay fever season
3	L. G.	24	10	2.4	I, II	Moderate root branch and central bronchial thickening	Negative	Mild asthma only during summer months
4	V. A.	11	12	1.3	I, II	Moderate hilar and root branch thickening	Negative	Mild perennial asthma. Occasionally severe asthma. Takes epinephrine
5	D. Z.	13	12	1.6	I, II	Negative	Moderate membranous infiltration of right antrum; slight membranous infiltration of right ethmoid	Moderate asthma following hay fever season. Takes ephedrine
6	W. D.	26	13	3.4	None	Moderate root branch thickening	Pansinusitis, large polypi in both nostrils. Submucous resection and polypectomy performed	No severe asthma. Cough, wheeze and shortness of breath related to stuffed nose
7	E. S.	40	14	5.6	I, II, III	Moderate root branch thickening	Hyperplastic thickening of right antrum, both ethmoids, and both frontals	Mild hay fever. Uses epinephrine and aminophylline frequently for severe asthma
8	I. P.	29	15	4.4	I, II	Moderate old root branch and central bronchial thickening	Slight hypertrophic thickening of antra and ethmoids	Mild asthma during and following hay fever season
9	M. M.	12	15	1.8	I, III	Old hilar, root branch, and central bronchial thickening	Marked membranous infiltration of antra and ethmoids	Asthma, mild. Shortness of breath on exertion
10	L. D.	41	16	6.6	None	Moderate hilar and root branch thickening	Moderate antral and ethmoidal infiltration	Moderate or severe asthma following frequent sinusitis
11	D. G.	4	16	0.6	I, II	Moderate root branch thickening	Negative	Mild asthma from May to October, and occasionally during winter months. Patient neurotic—uses ephedrine and epinephrine frequently

*I = Hay fever.
†II = Positive skin tests.
‡III = Positive family history.

12	F. S.	45	16	7.2	I, II	Slight root branch thickening	Slight membranous infiltration of antra and ethmoids	Asthma follows sinusitis. Takes epinephrine and aminophylline for severe asthma. Had nose operation
13	F. W.	62	16	10.0	I	Slight root branch thickening	Slight membranous thickening of ethmoids	Mild asthma every year from January to April
14	A. S.	8	17	1.4	I, II, III	Negative	Slight congested edema of right antrum	Mild asthma and cough following hay fever season. Mainly nose trouble
15	I. B.	14	17	2.4	None	Slight hilar and lower root branch thickening	Negative	Mild wheezing previous six months following nose colds
16	J. U.	29	18	5.2	I, II, III	Negative	Slight membranous infiltration of right ethmoid	Hay fever, mild. Asthma chiefly during winter months following head colds
17	M. B.	3	19	0.6	II, III	Negative	Moderate membranous infiltration of left antrum	Slight wheezing usually in winter months following a head cold
18	J. W.	12	20	2.4	None	Emphysema both lungs. Moderate accentuation of hili and central trunk branches	Pansinus hyperplastic thickening	Asthma all year round. Severity depends upon degree of sinus infection
19	W. L.	3	20	0.6	I, II, III	Slight old central thickening with faint calcified flecks in right hilus	Moderate membranous infiltration of right antrum. Slight infiltration of left antrum and right ethmoid	Mild asthma and clogged nose all year round
20	M. G.	12	20	2.4	II, III	Moderate hilus and root branch thickening	Hypertrophy of turbinated bones	Mild to moderate asthma all the time. Worse in winter months
21	J. L.	29	21	6.1	I, II	Moderate root branch thickening	Negative except for diminished nasal ventilation	Moderate perennial asthma aggravated by pollens during summer months
22	R. B.	28	21	6.0	None	Moderate root branch thickening	Slight infiltration of right antra and ethmoids	Sneezing and mild asthma all year round
23	M. J.	8	22	1.8	I, II, III	Negative	Slight membranous infiltration of right antrum and both ethmoids	Mild asthma, hay fever, and sinusitis
24	I. S.	10	23	2.3	II	Negative	Hypertrophy of turbinated bones	Mild to moderate asthma with sneezing and running nose. Takes ephedrine
25	F. G.	22	23	5.1	III	Moderate hilar and central root branch thickening. Slight emphysema	Hyperplastic thickening of antra and ethmoids	Moderate to severe asthma all year round related to nose. Uses ephedrine and epinephrine

TABLE I—CONT'D

NUMBER	CASE	SPUTUM VOLUME IN 24 HR. (ML.)	CHOLESTEROL IN SPUTUM		ALLERGIC CRITERIA	X-RAY OF LUNGS	X-RAY OF SINUSES	NATURE OF ASTHMA
			MG. PER CENT	MG. 24 HR.				
26	H. B.	20	23	4.6	I, II, III	Moderate root branch and central bronchial thickening	Moderate membranous infiltration of right antrum and ethmoid	Hay fever and mild asthma from June to October. Asthma in winter only following sinusitis
27	E. S.	31	24	7.4	II, III	Negative	Moderate membranous infiltration of right antrum; slight membranous infiltration of right ethmoid	Mild asthma all year round. Frequent sinus infections
28	T. R.	26	25	6.5	II, III	Negative	Moderate membranous infiltration of both antra; slight membranous infiltration of right ethmoid	Mild asthma, worse during winter months
29	Z. D.	22	27	5.9	II, III	Slight old central puerile type thickening	Moderate hyperplastic thickening of right antrum	Mild to moderate asthma. Chronic cough and wheeze. Frequent head colds
30	E. V.	23	27	6.2	None	Slight root branch thickening	Slight hyperplastic thickening of antra and ethmoids	Moderate asthma all year following nose colds
31	K. M.	28	27	7.6	None	Slight old hilar thickening	Slight congestive edema of right antrum and ethmoid	Mild asthma following frequent head colds especially in winter
32	J. S.	23	29	6.7	II, III	Moderate root branch thickening and pulmonary hypervascularization	Marked membranous thickening of right antrum and both ethmoids	Mild asthma all year round, with nasal obstruction, headache, and cough
33	M. S.	26	30	7.7	None	Negative	Moderate membranous infiltration of right antrum and both ethmoids	Perennial asthma, worse in winter months and early spring following colds
34	C. M.	52	31	16.0	None	Considerable hilar, root branch, and central bronchial thickening. Moderate dilatation beyond lower cornu mainly on the right	Slight antral and ethmoidal infiltration	Moderate asthma with cough and expectoration

35	G. C.	13	32	4.2	None	Moderate thickening at hilus and root radiating toward the periphery. Emphysema	Moderate membranous thickening of antra; slight membranous thickening of right ethmoid	Mild asthma following frequent nose colds. Dyspnea on exertion
36	C. M.	14	32	4.5	None	Moderate root branch and central bronchial thickening more noticeable toward the bases	Moderate thickening of antra	Mild asthma all year round following head colds
37	L. G.	19	32	6.1	I, II, III	Slight root branch thickening	Diminished nasal ventilation. Submucous resection several years previously	Moderate asthma only during summer months. Nose colds during winter
38	J. T.	29	33	9.6	None	Slight root branch thickening. Pulmonary hypervascularization	Moderate membranous infiltration of ethmoids and right antrum	Perennial asthma but much worse in winter following sinusitis
39	M. D.	3	33	0.9	None	Interstitial changes at the roots of both lungs extending throughout the parenchyma	Moderate membranous infiltration of antra and ethmoids	No severe asthma but continuous cough and wheeze during winter months. Takes ephedrine mixtures
40	A. C.	44	34	15.0	I, II, III	Slight old central thickening	Congestive edema of ethmoids	Mild hay fever, but severe following frequent nose colds. Takes adrenalin often
41	B. P.	44	34	15.0	None	Negative	Moderate membranous infiltration of left antrum; slight membranous infiltration of left ethmoid. Polypoid middle turbinated bones	Moderate asthma; takes ephedrine occasionally; severe asthma requiring epinephrine
42	W. K.	18	36	6.6	None	Moderate old root branch and central bronchial thickening mainly on the right. Lower lobes emphysematous	Moderate hyperplastic sinuses	Mild asthma associated with sinusitis mostly in the winter
43	D. S.	7	36	2.5	II, III	Moderate thickening of hili and central trunk branches	Hyperplastic thickening of antra and ethmoids. Middle turbinated bones swollen	Mild asthma with moderate sinus involvement
44	L. M.	17	36	6.2	None	Moderate root branch thickening	Moderate membranous infiltration of right antrum and ethmoids	Moderate asthma with cough. Taking ephedrine

TABLE I—CONT'D

NUMBER	CASE	SPUTUM VOLUME IN 24 HR. (ML.)	CHOLESTEROL IN SPUTUM		ALLERGIC CRITERIA	X-RAY OF LUNGS	X-RAY OF SINUSES	NATURE OF ASTHMA
			MG. PER CENT	MG. 24 HR.				
45	A. A.	29	38	11.1	None	Marked hilar and root branch thickening especially at the right base	Marked membranous thickening of ethmoids and antra	Moderate asthma all year round. Related to nose. Takes ephedrine for relief. Severe asthma; takes adrenalin
46	G. T.	80	44	35.4	None	Moderate hilar and root branch thickening	Pronounced antral and ethmoidal infiltration	Severe continuous cough with profuse expectoration. Dyspnea on exertion. Emphysema. Uses large amounts of ephedrine and adrenalin
47	J. N.	--	50	--	None	Marked hilar, root branch, and central bronchial thickening diminishing toward the periphery. Further moderate dilatation toward the bases	Hypertrophy and polypoid degeneration of nasal mucosa with postnasal drip	Mild asthma and cough usually during the winter months until hospitalized, when sputum was examined. Epinephrine and aminophylline given
48	R. B.	11	50	5.3	None	Marked hilar and root branch thickening especially toward right base. Emphysema	Moderate membranous thickening of right antrum and left ethmoid	Perennial moderate asthma associated with chronic sinusitis. Chronic bronchitis of long standing. Takes ephedrine
49	M. F.	12	52	6.2	None	Moderate root branch thickening mainly lower cornu	Chronic membranous infiltration of maxillary antra	Moderate bronchial asthma all year round following frequent head colds. Takes ephedrine mixtures for relief
50	I. W.	3	53	1.5	None	Moderate root branch thickening	Pansinusitis with profuse postnasal discharge	Moderate asthma all year round accompanied by sneezing and cough. Takes large amounts of ephedrine
51	S. B.	27	55	14.8	None	Moderate root thickening both lungs. Marked general pulmonary vascularization	Hyperplastic pansinusitis	Continuous severe asthma; uses excessive amounts of ephedrine and aminophylline

TABLE II. REDETERMINATION OF CHOLESTEROL VALUES IN SPUTUM

NUMBER	CASE	SPUTUM VOLUME IN 24 HR. (ML.)		CHOLESTEROL IN SPUTUM				CLINICAL STATUS AT SECOND DETERMINATION
				FIRST RESULT		SECOND RESULT		
		FIRST RESULT	SECOND RESULT	MG. %	MG. IN 24 HR.	MG. %	MG. IN 24 HR.	
1	S. S.	20	12	7	1.4	22	2.7	Moderate asthma with sinusitis
4	V. A.	11	23	12	1.3	36	8.1	Severe asthma. Epinephrine taken
5	D. Z.	13	17	12	1.6	41	6.9	Moderate asthma after hay fever season. Epinephrine taken
6	W. D.	26	22	13	3.4	17	3.7	No change in condition
7	E. S.	40	8	14	5.6	56	4.4	Severe continuous asthma. Epinephrine and aminophylline taken
9	M. M.	12	11	15	1.8	8	0.9	Improved with treatment
11	D. G.	4	14	16	0.6	35	4.9	Cough and slight asthma with hay fever symptoms. Neurotic. Using large amount of epinephrine
12	F. S.	45	8	16	7.2	30	2.4	Severe asthma with sinus infection. Ephedrine and epinephrine taken
16	J. U.	29	26	18	5.2	14	3.6	No change in condition
21	J. L.	29	20	21	6.1	24	4.8	No change in condition
24	I. S.	10	5	23	2.3	41	2.0	Moderate asthma with coryza. Ephedrine taken
29	Z. D.	22	17	27	5.9	30	5.1	No change in condition
35	G. C.	13	10	32	4.2	35	3.5	Improved with treatment
38	J. T.	29	22	33	9.6	20	4.4	Improved with treatment
43	D. S.	7	7	36	2.5	38	2.6	No change in condition
44	L. M.	17	18	36	6.2	36	6.4	No change in condition. Iodides taken for one week before second determination
47	J. N.	--	8	50	--	34	2.7	Condition improved following treatment in hospital

that showed higher determinations of 32 and 34 mg. per cent had associated chronic respiratory infections (Cases 37 and 40, Table I).

Most of the patients showing 20 to 30 mg. per cent sputum cholesterol values were mixed cases, in that they were skin sensitive and had chronic respiratory infections.

The quantity of cholesterol expectorated in twenty-four hours ranged from 0.6 to 16 mg., and this amount was exceeded in only one patient (Case 46, 35.4 mg.) who expectorated 80 ml. in twenty-four hours whereas the average volume expectorated in the fifty cases was 22 milliliters. This patient had extensive sinus infection with profuse postnasal discharge. In most of the patients the sputum cholesterol ranged from 1 to 10 mg. per twenty-four hours. It was surprising that this twenty-four-hour sputum cholesterol fell within a 1 to 10 mg. range since the twenty-four-hour sputum specimens ranged from 3 to 80 ml. and contained 0.06 to 0.5 mg. per milliliter. A review of the literature fails to disclose any twenty-four-hour sputum cholesterol values in infective chest conditions.

The cholesterol content of the sputum was decidedly increased in patients who had chronic, persistent asthma and who were therefore, resorting to large amounts of epinephrine and ephedrine for relief (Cases 44 to 51, inclusive). The age of the patients studied varied from 15 to 66 years, and there was no correlation between various age groups and cholesterol values.

Cholesterol determinations repeated on the sputa of seventeen patients after an interval of from four to six months (Table II) showed that the cholesterol content varied in relation to the clinical changes in the patient's condition.

DISCUSSION

Cholesterol is an essential constituent of all cells and fluids of the body. The lung tissues are known to be rich in it.[6] Accompanying diseases of the

respiratory tract, there is tissue destruction with the formation of sputum. It is believed that sputum contains cholesterol in an amount depending upon the extent of cellular autolysis.[4] Rémond, Colombies, and Bernardbieg[7] have demonstrated that cholesterol from all tissues of the body is retained or destroyed partly in the liver and partly in the lungs. Sputum cholesterol determinations have been made in various pulmonary diseases, especially pulmonary tuberculosis, but so far little has been done on the sputa of asthmatic patients.

Examination of the sputa of fifty-one asthmatic patients showed that the amount of cholesterol was related to the severity of the clinical symptoms and, by implication, to the extent of bronchopulmonary destruction. High sputum cholesterol values were noted only in individuals whose symptoms were caused or aggravated by infection of the bronchi and paranasal sinuses. Such high values were not evident in patients with a purely skin-sensitive type of asthma. Repeated sputum determinations showed variations (increases or decreases in cholesterol) in accordance with the change in the patient's condition. Such observations seem to indicate that repeated analysis of the sputa for cholesterol may be a method helpful in evaluating the status of the asthmatic patient. However, these cholesterol studies are of value only when appraised in conjunction with the clinical sequence of events and the employment of all other necessary laboratory data.

The sputum cholesterol increase in the chronic asthmatic patient may be due in part to the frequent use of epinephrine and other pressor acting substances. Onizawa[8] has shown that the lung is always enlarged after repeated epinephrine injections with an increase in the amount of tissue cholesterol. It is possible that the pressor acting substances employed for the relief of severe asthmatic attacks cause an extrusion of cholesterol from the bronchomucosal walls.

SUMMARY

1. Cholesterol values on the sputa of fifty-one patients suffering from bronchial asthma ranged from 7 to 55 mg. per cent.

2. The amount of cholesterol varied with the severity of the clinical symptoms.

3. High sputum cholesterols were noted in the infective or skin-negative type of bronchial asthma (25 to 55 mg. per cent).

4. The total amount of cholesterol expectorated in twenty-four hours ranged from 1 to 10 milligrams.

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ATOPIC SENSITIVITY TO CAROID (PAPAIN)

Report of a Case With Discussion of Some of the Properties and Uses of the Drug

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THE recent observation of a patient who had developed intense symptoms on exposure to Caroid has prompted me to present the case and to survey the pertinent literature.

Caroid is a proprietary name for papain, *United States Dispensatory*, twenty-third edition. Papain contains proteolytic enzymes and is derived from the papaya tree *(Carica papaya)*. The drug is also known as papayotin and papoid.

Allergy to this substance has been reported in the past. Eyermann[1] described the case of a druggist whose vasomotor rhinitis was due to exposure to caroid. The scratch test was positive. The patient's symptoms were reproduced by experimental ingestion and by an overdose during hyposensitizing injections. Walzer[2] mentioned a patient, sensitive to caroid and pancreatin, whose skin reacted to these in extremely high dilution. Beecher[3] reported the case of a druggist who had vasomotor rhinitis and asthma when handling dry caroid. The scratch test was positive, and tasting a solution brought on acute swelling of the lips. Hyposensitization gave improvement. Beecher also mentioned briefly another druggist who had severe asthma on exposure to caroid, being found unconscious therefrom on two occasions, and a third druggist who had angioneurotic edema and dyspnea after ingestion of caroid. Maisel[4] studied the case of a pharmacist who had vasomotor rhinitis when working with powdered enzymes. He tested the patient with caroid and produced a 2 plus reaction, but could demonstrate no reagins. Both Walzer and Maisel remark that allergy to caroid is not uncommon.

These six cases were the only ones found in a careful search of the literature. They have occurred chiefly among pharmacists, whose exposure presumably was to the dried powder and who were probably sensitized by the common route of inhalation. Sensitization by ingestion might occur, as the substance has a number of uses which will be described later. The case reported herewith, however, was apparently sensitized neither by inhalation nor by ingestion, and therefore presents possibilities not heretofore appreciated.

CASE REPORT

A married woman, aged 41 years, was first seen on April 8, 1944, complaining of severe paroxysmal cough, vasomotor rhinitis, and dyspnea. Her history in brief was as follows:

In July, 1942, she underwent bilateral vein ligations for varicosities of the legs. One wound sloughed open, and, in order to clear up the slough, caroid powder was dusted on for three or four weeks. No untoward local or constitutional symptoms were noted from this treatment, and the wound healed eventually. The history of this exposure to caroid was not obtained until later in her illness.

About March 21 or 22, 1944, her husband for the first time began the use of caroid tooth powder on the advice of his dentist. On March 24, the patient had a rather sudden onset of sneezing and coryza, and her eyes became red and the eyelids swollen. On March

30, a paroxysmal cough developed which rapidly increased in frequency and intensity, associated with dyspnea and orthopnea.

When seen on April 8, the only indications of allergy in her past had been the occurence since childhood of bronchial colds in the winter and of some sneezing when exposed to certain cosmetic powders. No family history of allergy was elicited.

Examination showed a dry cough with dyspnea. The temperature was 99° F.; pulse, 96; respirations, 26; and blood pressure, 122/80. There were a moderate number of asthmatic wheezes in the lungs. The rest of the examination was essentially negative. X-rays of the chest showed the heart and lungs to be normal. X-rays of the paranasal sinuses showed no fluid or thickened membrane. There were 18 per cent eosinophiles in the differential blood count, and two specimens of sputum showed an eosinophilia. One hundred fifty direct intradermal tests to pollens, molds, inhalants, and foods yielded a number of moderate to marked reactions, the most significant of them being to orrisroot and mattress and house dusts, with lesser reactions to some other inhalants and to a few foods.

Symptomatic treatment and the most careful elimination of the then known reacting inhalants and foods did not control her asthma, which became increasingly severe and for which she was admitted to the Buffalo General Hospital on three occasions. On all admissions her asthma improved greatly before discharge. It recurred severely at home, however, within a few days following her first and second discharges from the hospital.

Just before her third hospital admission, when making a visit to her home to administer epinephrine, I discovered a container of caroid tooth powder in the bathroom. The patient did not use this brand, but she then recalled that her husband had begun to use it shortly before the onset of her symptoms. She also remembered an incident a few days past, when she had had a particularly sharp paroxysm of asthma after cleaning her teeth for the first time with her husband's powder. She was positive that she had had no contact with caroid prior to March 21 or 22, 1944, except for the use of it in the wound in July, 1942.

During her third stay in the hospital, all traces of the caroid tooth powder were removed from the home. Since her return there she has had no further asthma. Hyposensitizing injections of orrisroot and dust were begun on June 27, and have been continued uneventfully to the present.

A quantity of powdered caroid was secured and an extract was prepared in Coca's solution after defatting.

The patient was tested intradermally with about 0.02 c.c. each of 1:500 and 1:50 dilutions of this extract. The surrounding skin immediately flushed strongly. Within one minute the patient complained that her hands felt hot and her face flushed. She was placed recumbent, where she rapidly became confused, pale, and sweating. She vomited, her respirations became labored, her pulse became imperceptible, and she lost consciousness. Epinephrine was immediately injected beneath the two skin-test sites and a tourniquet was applied above them. More was injected into the other arm, followed by massage of the areas to speed the dispersal of the drug. One-half hour after the tests her systolic blood pressure was 60 mm. Hg, but the pulse had become palpable.

During the succeeding two hours, the pulse strengthened, her mind cleared, and recovery took place slowly. Two and one-half hours after the tests her pulse was 90, the blood pressure 130/80, and the patient felt well except for some weakness.

She had severe urticaria for the following five days. On the third day after testing redness and superficial necroses the size of a dime appeared at the test sites, and her arm swelled from shoulder to forearm. The swelling lasted three days, and the scabs fell from the necrotic areas nine days later. Redness at the test sites was followed after several weeks by pigmentation which was still present at the time of this report. Subcutaneous nodules persisted under the sites for four months.

REAGIN, PRECIPITIN, AND COMPLEMENT FIXATION STUDIES

On September 12, blood was obtained from the patient. Passive transfer was done on a nonallergic individual who had been shown previously to be a good receptor and who was skin negative by intradermal tests to caroid. Numerous sites were made with various dilutions of the patient's serum and were tested with serial dilutions of the caroid extract and with certain controls. No site was tested more than once. The results are given in Table I.

TABLE I. PASSIVE TRANSFER STUDIES

DILUTION OF PATIENT'S SERUM	DILUTION OF CAROID EXTRACT					
	1:50	1:500	1:5,000	1:50,000	1:500,000	1:2,500,000
Undiluted		+++++	++++	+++	+++	
1:5				+++	+++	++
1:25				+++	++	+
1:125				+++	++	±
1:625				++	+	0
1:3,125				+	0	0
1:15,625			+	±		
1:78,125			±	+		
Tests on Unsensitized skin	0	0	0	0		
Saline Control on Sensitized Site	Negative	8				

Doubtful reaction but not negative, ±; negative, 0; minimal definitely positive reaction, +; marked reaction + + + + +.

No reagins were demonstrated in the patient's undiluted serum to orris, feathers, ragweed, or carrot; control tests with these on unsensitized skin of the receptor were also negative.

Precipitin tests were done with the undiluted serum and with various dilutions of the same against serial dilutions of the caroid extract. No precipitins were demonstrated.

Complement fixation tests were done, using a 1:5 dilution of the patient's inactivated serum with serial dilutions of the caroid extract plus guinea pig complement against the usual antisheep cell amboceptor and 4 per cent sheep cell suspension, and with suitable controls. No deviation of complement was shown.

From the above studies, it is apparent that the patient had a true atopic sensitivity to caroid (papain), with specific reagins in high concentration in her blood. The skin was sensitized to such a degree that typical Arthus necrosis occurred at the skin-test sites. The extremely severe constitutional reaction on testing demonstrates again the need for the utmost caution and the use of weak dilutions when testing with untried allergens*

This patient had evidently been sensitized by absorption of the caroid antigen through the wound in July, 1942. The American Ferment Company, manufacturer of the drug, in response to a query, reported that besides the caroid from *Carica papaya,* the tooth powder contained oil of peppermint and other "standard ingredients which are considered to be hypo-allergic." The caroid itself contains "no added substances of plant or other origin." The questions arise therefore as to other evidences of the antigenicity of papain (caroid) and as to its uses which would constitute sensitizing and "shocking" exposures.

ANTIGENICITY OF PAPAIN

The plant *Carica papaya,* from the latex of which papain is derived, is a dicotyledonous angiosperm belonging to the family *Archichlamydeae,* genus *Caricaceae.* It has no near botanical relatives in use.[5]

Animal experimentation by several workers has indicated that papain is a very active antigen. It can induce anaphylaxis in dogs[6] and in guinea pigs.[7-9] Specific precipitins and complement fixing antibodies follow its injection into rabbits.[7, 9] Specific sensitization of the uterus can be shown by the Schultz-Dale technique in injected guinea pigs.[9] The antigen in papain is not the same as that in the proteolytic enzyme pepsin.[9] Papain contains powerful proteolytic enzymes and has certain other actions.[10-13] It has been prepared in crystalline form.[14]

*Nitrogen determinations on the 2 per cent extract, which had not been done at the time of the testing, showed: total nitrogen, 0.99 mg. per cubic centimeter and phosphotungstic acid precipitable nitrogen, 0.76 mg. per cubic centimeter.

MEDICINAL USES OF PAPAIN

There are a number of parenteral uses of papain reported in the literature, all of which could constitute either sensitizing or "shocking" exposures. Intraperitoneal instillation of a sterile solution of papain (up to 1 liter) for the prevention of postoperative adhesions was used in a large number of patients in the 1930's.[15-17] It has been used topically in solution for the treatment of sloughing wounds.[18] It is said to be very effective in clearing up the discharge of chronic purulent otitis media[19] and for dissolving the eschar of burns[20] and the membrane of diphtheria.[7] It has also been used through the bronchoscope for loosening the exudate in membranous tracheobronchitis. It has been used locally for the treatment of carbuncle[21] and by injection of the synovial sac in the treatment of ganglion,[22] the latter with serious results.

No evidence that ingestion of papain can induce sensitivity has been disclosed. Its ingestion, however, has elicited symptoms in already sensitized persons.[1, 3] For this reason the following list of oral preparations containing papain[23] may be useful:

All the "Caroid" preparations, American Ferment Co.
Caripeptic Liquid and "Carica" preparations, The Upjohn Co.
Bisodol.
Digestone Elixir, Robert McNeil.
Elixir Caricans, Fraser Tablet Co.
Protenzamyl, R. J. Strasenburgh Co.
Liquor Diastos, Sharp and Dohme, Inc.
Panpasoda, G. D. Searle and Co., Inc.
C. M. S. Compound, Walker Pharmacal Co.

There are probably other oral preparations containing it as it seems to have some popularity as a digestant.

COMMERCIAL AND INDUSTRIAL USES OF PAPAIN

The fruit of *Carica papaya* (also called papaya or pawpaw) has considerable popularity for eating purposes in regions where it is available (Tropical America, West Indies, Florida, California, Ceylon, and Malaya). The juice is canned and sold at delicatessen and special food stores in the United States. It is entirely distinct from the North American pawpaw *(Asimina triloba)*.

The proteolytic properties of papain have been applied to a variety of uses. Much of the papain imported into the United States is used in preparations for rapidly tenderizing tough meat.[14] It acts more evenly when mixed with ground meat. Since the enzyme is relatively resistant to heat it is smeared on, or mixed with, the meat just before cooking and acts during the cooking.

Papain has been used for many years in the brewing industry for making "chillproof" beer, preventing turbidity on cooling by digesting the traces of protein dissolved in the beer.[14] It has been estimated that 80 per cent of American beer is so treated. The dilution, however, is very weak. Papain is used in the tanning industry for bating skins and hides,[24] and the latex is used in chewing gum manufacture.[5]

Of incidental interest is the fact that papain will inactivate ragweed pollen extract resistant to animal proteases.[25] It will inactivate several bacterial toxins.[26] Animal proteins digested by papain apparently form excellent bases for culture media.[27] The practicability of these uses would seem to be doubtful, however, because of its high antigenicity.

DISCUSSION

From the experimental work referred to and from the several case reports, it is evident that papain is actively antigenic and is capable of sensitizing human beings both by inhalation of the dry powder (apparently the common mode) and by absorption through granulation tissue. This sensitivity is of the atopic type, not a true drug-sensitivity. I believe that the atopen probably is related to the water-soluble plant extractives and is independent of the actual proteolytic enzymes present, although this question will bear further study.

Most of the cases reported heretofore have been in pharmacists, who were presumably sensitized by inhaling the powdered papain. In recent years the introduction of papain in the form of caroid tooth powder has created the conditions for sensitizing persons in the general population by inhalation.

Through its use medicinally, papain has elicited symptoms in sensitized persons by inhalation, by ingestion, by injection, and by local application. It may be an excitant of symptoms through exposure to it in the brewing and tanning industries, in chewing gum, and in food preparations.

How common this sensitivity is and how widespread is the exposure we do not yet know. I have tested intradermally forty patients with dilutions of 1:50,000, 1:10,000, 1:5,000, and 1:1,000 of caroid without untoward results. Four of these patients (10 per cent) gave moderate skin reactions and seven more gave slight reactions, a total of eleven (27 per cent). Six patients admitted the use of caroid tooth powder. One of these, a pharmacist, gave a moderate reaction, and two others gave slight reactions. The significance of these reactions has not been finally determined.

SUMMARY

1. Papain is an active antigen.

2. Sensitivity to it in human beings is atopic in type and is not uncommon.

3. Its several uses medicinally, industrially, in dentifrice (caroid) and chewing gum, and in food preparation create exposures in the general population which the allergist must keep in mind.

I wish to express my appreciation to Dr. Ernest Witebsky, Professor of Bacteriology and Immunology, University of Buffalo Medical School, and Chief of the Bacteriologic and Serologic Laboratories, Buffalo General Hospital, for his courtesy in extending to me the facilities of his laboratories, and to Dr. Carl E. Arbesman, Assistant in Medicine and in Immunology, who carried out the precipitin and complement fixation tests.

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SKIN SENSITIVITY IN THE AGED—FATALITY FOLLOWING INTRADERMAL TESTS

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CONSTITUTIONAL reactions following intradermal testing or hypodermic injections have been recognized for some time. Cooke[1] (1922) and Lamson[2] (1929) were among the earliest to report fatalities after intradermal testing.

The cases reported have usually been in younger patients in whom the skin is supposed to be more reactive than in the aged. We are reporting a death following intradermal testing in a woman, 78 years of age, who had marked positive reactions to many of the allergens with which she was tested. The skin of elderly people is usually considered to be relatively inactive and positive reactions generally not to be expected, but we were able to find in the literature only two references to this subject. Fineberg[3] wrote, "An atrophic skin, a skin with poor circulation or the skin of the aged may be so diminished in reactivity that what would be ordinarily moderate reactions may become negative." Tuft[4] stated that "especially in older individuals or in those who have had their condition for some time, the skin is likely to be of the nonreactive type."

CASE REPORT

The patient, Mrs. C., a small, elderly-appearing but mentally active widow, aged 72 years, was first seen at the Allergy Clinic of the Syracuse Free Dispensary in January, 1938. She gave a history of asthma since the age of 4 years, usually occurring in the fall or winter

when she was confined indoors in the single room in which she lived. The asthma had become worse in the previous October. She also complained of cough, dyspnea, and palpitation. Milk, pork, and cabbage were said to be responsible for attacks; also the presence of a cat. Respiratory infections made her worse.

Examination showed a thin, small woman, with considerable kyphosis; her weight was 75 pounds, and her blood pressure 120/80. The heart was enlarged to the left. There was a systolic mitral murmur and accentuation of the aortic second sound. The chest was hyperresonant, but no râles were heard. Some peripheral arteriosclerosis was noted; no dependent edema. Blood and urine were not remarkable. Two Wassermann reactions were partially positive.

X-ray of the chest showed considerable peribronchial thickening; of the sinuses, relatively good ventilation. Intradermal skin tests, both with inhalants and foods, disclosed a surprising number of positive reactions, many of them quite large.

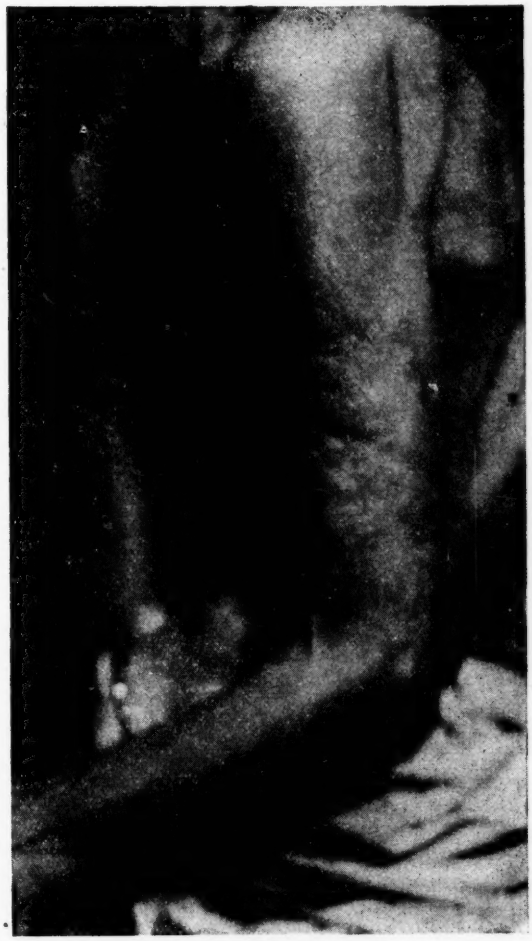

Fig. 1.—Mrs. C. Positive intradermal tests, inhalant group, made in February, 1938, when the patient was 72 years of age.

Environmental precautions were prescribed. She was advised to avoid some of the positive foods, and was treated with gradually increasing doses of house dust and stock respiratory vaccine. She improved with treatment and was finally able to take 1 c.c. each of concentrated dust and vaccine. The general condition and asthma showed considerable improvement, and she gained several pounds. This improvement was maintained, and she took no treatments from March, 1941, until May, 1944, when, at the age of 78 years, she complained of increased asthma, weakness, and loss of weight. Dust and vaccine treat-

ment was resumed May 2, 1944. Skin testing had not been done for six years, and, on May 23, 1944, seventeen intradermal retests were made with the following:

	Protein Nitrogen Units		*Protein Nitrogen Units*
Coffee	1-10	Horse dander	1,000
Kapok	1,000	Goat dander	1,000
Rabbit dander	1,000	Karaya gum	1%
Feathers	1,000	Flaxseed	1,000
Orrisroot	1,000	Cat dander	1,000
Cottonseed	1,000	Silk	1,000
Dog dander	1,000	Tobacco	1,000
Cow dander	1,000	Pyrethrum	1,000
		Sheepwool	1,000

Small amounts of testing material were used—0.01 to 0.02 cubic centimeters. She was also given a treatment injection of house dust, 0.35 c.c. and stock vaccine 0.3 cubic centimeters. In about five minutes she began to cough and developed asthma of moderate severity. Epinephrine was at once administered subcutaneously, and an effort was made to measure the skin positives which were very numerous and fairly large. The patient suddenly became cyanotic and collapsed into unconsciousness. Epinephrine solution was given by vein, oxygen was administered, and artificial respiration performed. The pulse remained regular and fairly strong for several minutes, but the respirations became more feeble. Epinephrine was then given into the heart, but respiration was not resumed, the pulse ceased, and the patient expired about fifteen minutes after the skin tests were inserted. An autopsy was not permitted.

This patient, in a previous year, 1938, had been tested with similar extracts and had received dust and vaccine injections in much larger doses, yet on this particular day she unexpectedly failed to tolerate them.

SUMMARY

1. In the aged, atrophic as the skin may appear to be, the reactivity to skin tests may be very acute. The reaction is an individual one and depends upon the sensitivity of the skin, organs, and tissues.

2. Although the allergic condition had existed for seventy-four years, it did not render the skin nonreactive or diminish its sensitivity.

3. The aged require the same meticulous care in testing and treatment as patients of any age group.

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A SIMPLE METHOD FOR PREPARING STRAINED MEAT FORMULAS

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THE successful use of strained meats as a milk substitute was pointed out by Glaser[1] who used Rowe's[2] formula. The extensive detailed method of preparation, which required production by a large commercial firm,[1] was described.

It was further stated that these formulas would not be available until after the war. There is a definite need now for the use of milk formula substitutes because of the difficulty of adequate and proper feeding of infants with both milk and soybean sensitivity. This is becoming an increasing problem. Other substitute milks have been shown to be inadequate[3-5] or unsatisfactory, while some have been difficult to prepare, and this discouraged their use.[1]

I have found that meat formulas can be prepared easily and inexpensively at home and successfully used. They can be made available now and do not need to await postwar commercial manufacture.

The method of preparation is as follows: Measure 34 ounces of water in the top section of a double boiler, and bring to a boil. Into one container measure 2⅔ tablespoonfuls of dextrose, ½ teaspoonful of salt and 1 teaspoonful of calcium. In another container dissolve 2½ tablespoonfuls of tapioca flour in 3 ounces of cold water. Stir the sugar mixture, then the flour mixture, into the boiling water. Place immediately over the bottom part of a double boiler containing boiling water and cook for forty-five minutes, stirring occasionally to prevent lumping.

The well-done meat should be cut from the bone and freed from fat and gristle. Next, put it through a meat grinder. Then, measure 1⅛ cupfuls of the ground meat and add sufficient liquid to enable the machine* to liquefy it. (The meat juice, after the fat has been removed, may be used as part of the liquid.) Estimate the number of days the meat is to be used and apportion the juice accordingly, so that there will be the same amount for each day's formula. To determine the amount of fluid necessary to liquefy meat the following is suggested. Measure the ground meat into a container marked in cups or ounces (do not pack). Add the juice and boiled water until the liquid line reaches the mark previously reached by the meat (1⅛ cups in this case).

Pour into a liquefier* and allow the machine to run until the meat mixture pours easily through a medium coarse strainer, leaving little or no residue. Add 2½ teaspoonfuls of oil to the meat while it is still in the liquefier. Blended this way it will not rise to the top as it might if added later. When the tapioca mixture has cooked for forty-five minutes, stir in the meat and cook for about ten minutes more to sterilize the formula. Pour into sterilized bottles, stirring frequently to prevent the meat from settling to the bottom, thus keeping the contents equal in each bottle. Add water to make up for that which has boiled away so that the original volume is retained (in this case about 46 ounces). Before using, warm and shake well.

Some helpful suggestions are as follows:

1. The larger cuts of meat of the better grades which have been roasted a long time in a slow oven are the easiest to liquefy.

*Waring Liquefier, Monarch-Knapp Liquidizer, General Electric Liquefier, etc.

2. Allow about 1 pound of meat for each day's formula for older infants.

3. If hot water is used, the meat will liquefy more easily.

4. In increasing the amount of formula to meet the baby's needs, do not increase the amount of salt in proportion to the other ingredients, or the formula will taste too salty.

5. A simple way to find out how much water to add to the formula is to pour the formula into the number of bottles that are to be used, putting an equal amount into each bottle. Then add sterile water to the contents of each bottle to bring it up to the amount of liquid originally in the formula before cooking. For example: In bottling the amount given, divide the cooked formula between six bottles and then add water to make 7½ ounces in each bottle, making a total of 45 ounces or approximately the amount used to start with.

6. If a double boiler in a 2-quart size is not available, two pans that fit closely together with enough difference in height to allow for boiling water in the bottom pan can be used.

TABLE I. STRAINED MEATS (ROWE) USED FOR COW'S MILK FORMULA SUBSTITUTES

	WEIGHT GM.	MEASURE	CHO	PROTEIN GM.	FAT GM.	CALORIES	Ca GM.	P GM.	Fe GM.	Cl AS NaCl
Strained lamb P—12.23 per cent F—11.17 per cent	270	1⅛ cups	--	33	30	402	0.11	2.07	.015	
Strained beef P—10.74 per cent F—10.07 per cent	307	1¼ cups	--	33	30	402				
Sesame or soy oil	10	2½ tsp.	--	--	10	90				
Sugar (cane or beet)	30	2⅔ tbs.	30	--	--	120				
Potato starch flour 83 per cent CHO or	24	2⅓ tbs.	20	--	--	80				
Tapioca flour 88 per cent CHO	23	2⅓ tbs.	20	--	--	80				
Calcium carbonate 40 per cent Ca	3	1 tsp.	--	--	--	--	1.20	---	---	---
Sodium chloride	1.75	½ tsp.	--	--	--	--	---	---	---	1.75
Water q.s. to 1,000 c.c.		4½ cups	--	--	--	--	---	---	---	---
Total for 1,000 c.c.			50	33	40	692	1.31	2.07	.015	1.75
Or 100 c.c. per cent			5.0	3.3	4.0	69.2	0.13	0.20	.0015	0.175
The above formula compared with whole cow's milk (Sherman and Bridges)			5	3.3	4.0	69	0.12	0.09	.0002	0.175
Human milk (Bridges)			6.5	1.5	3.3	61.7	0.04	0.01	.0001	0.058

SUMMARY

1. Strained meat formulas can be made available now.

2. They can be prepared readily and economically in the home and can be successfully used.

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3. Wolpe, L. Z., and Silverstone, P. C.: A Series of Substitutes in the Treatment of Allergies, J. Pediat. **21**: 635, 1942.
4. Hill, L. W.: Amino Acids as a Source of Nitrogen for Allergic Infants, J. A. M. A. **116**: 2135, 1941.
5. Finkelstein, L. O.: Mohnmilch als Säuglingsnahrung; vorläufige Mitteilung, Nohrung, Ztschr. f. Kinderh. **48**: 552, 1929.

American Academy of Allergy

NEWS AND NOTES

Report of the Nominating Committee

Article III, Section 3, of the Constitution reads as follows: "Election of Officers.—The president shall appoint a Nominating Committee consisting of three fellows, which committee shall report its recommendations to the secretary. The report of the Nominating Committee shall be submitted to the fellows in writing or by publication in the official Journal at least two months prior to the annual meeting. Nominations can also be made by a petition signed by ten fellows and sent to the secretary at least one month prior to the annual meeting.—A majority vote of fellows present at the annual meeting shall constitute an election."

Pursuant to the above section, the Nominating Committee, consisting of Drs. Charles H. Eyermann, Alan Cazort, and Mary Loveless, has submitted the following nominees for the next annual election.

For President	Dr. Stearns S. Bullen
For Vice-President	Dr. Will C. Spain
For Secretary	Dr. Karl D. Figley
For Treasurer	Dr. Leo H. Criep

Annual Meeting

As this issue of the Journal goes to press there is reasonable probability that the second annual meeting will be held in Chicago, December 10 and 11. Each member and fellow of the Academy will be notified promptly as soon as the decision of the Office of Defense Transportation has been received. Papers to be submitted for presentation should be forwarded to the secretary immediately. Those selected by the Program Committee will be announced in the November issue of the Journal. The complete program and announcement of the guest speakers will be published at that time.

The local committee on arrangements has reserved space for the meeting at the Palmer House in Chicago.

The Program Committee has completed most of its work. Dr. M. Mathews Robison, of Houston, Texas, a prominent otolaryngologist, will be one of the guest speakers. Dr. George Stakman of the University of Minnesota, a renowned authority on fungi, will be the other guest speaker. A review of the topic of infectious asthma will be introduced by short talks on the recognition, the immunology, the medical management, and the surgical management. This will be followed by an "information please," during which questions will be answered by the speakers plus some well-informed "experts."

The Orientation Course in clinical allergy offered by the School of Medicine, University of Pittsburgh, under the sponsorship of the American Academy of Allergy to be held in Pittsburgh, October 1 to 5, inclusive, will be conducted by the following faculty:

Harry L. Alexander, M.D., Professor of Clinical Medicine, Washington University School of Medicine, St. Louis, Mo.; Editor, Journal of Allergy.

Maurice Bruger, M.D., C.M., F.A.C.P., Associate Clinical Professor of Medicine, New York Post-Graduate Medical School, Columbia University; Chief of Division of Pathological Chemistry, New York Post-Graduate Hospital.

Milton Cohen, M.D., Cleveland, Ohio; Associate Editor, Journal of Allergy.

Mortimer Cohen, M.D., Associate Professor of Pathology, School of Medicine, University of Pittsburgh, Pittsburgh, Pa.

Leo H. Criep, M.D., Assistant Professor of Medicine and Lecturer in Immunology, School of Medicine, University of Pittsburgh, Pittsburgh, Pa.

Robert A. Cooke, M.D., F.A.C.P., Attending Physician and Director, Department of Allergy, Roosevelt Hospital, New York, N. Y.

Samuel M. Feinberg, M.D., Associate Professor of Clinical Medicine, Northwestern University, Chicago, Ill.

Frederick M. Jacob, M.D., Associate Professor of Dermatology, School of Medicine, University of Pittsburgh, Pittsburgh, Pa.

Richard A. Kern, M.D., Captain, MC(S), U.S.N.R.; Professor of Clinical Medicine, University of Pennsylvania, Philadelphia, Pa.

Howard C. Marcy, M.D., Assistant Professor of Medicine, University of Pittsburgh; Medical Director, Tuberculosis League Hospital, Pittsburgh, Pa.

E. R. McCluskey, M.D., Assistant Professor of Pediatrics, School of Medicine, University of Pittsburgh, Pittsburgh, Pa.

J. Homer McCready, M.D., Professor and Head of Department of Oto-Rhino-Laryngology, School of Medicine, University of Pittsburgh, Pittsburgh, Pa.

Louis Schwartz, M.D., Senior Surgeon, Medical Director, and Chief, Dermatoses Section, U. S. Public Health Service, Bethesda, Md.

W. C. Spain, M.D., F.A.C.P., Clinical Professor of Medicine, New York Post-Graduate Medical School, Columbia University; Chief of Allergy Clinic and Attending Physician, New York Post-Graduate Hospital.

Louis Tuft, M.D., Chief of Clinic of Allergy and Applied Immunology, Temple University Hospital; Associate in Immunology, Temple University School of Medicine, Philadelphia, Pa.

DIRECTORY OF THE AMERICAN ACADEMY OF ALLERGY

(Continued)

1924 **Davison, Hal McCluney,** 478 Peachtree St., N. E., Atlanta 3, Ga.
b 1891. A.B., Phar. B., Mercer U. 1911; M.D., Emory U. (Atlanta Med. Coll.) 1915; Cert. in Intern. Med. 1938 and in Allergy 1941; Att. Med., Ga. Baptist Hosp.; Assoc. Att. Med., Emory Univ. and Grady (Municipal) Hosps.; Consult. Med., Carrollton Clin.; Assoc. Med., Emory U. Med. Sch.; F.A.C.P.; A.C.A.; A.M.A.; A. Heart Assn.; A. Therap. Soc.; Assn. Study Intern. Secretions.

1931 **Denny, Earl Rankin,** 1102 Medical Arts Bldg., Tulsa, Okla.
b 1901. B.S., Indiana U. 1923; M.D., 1925; Lt. Col., M.C.; Chief, Med. Serv. Gardiner General Hosp.; F.A.C.P.; A.M.A.; M., South. Med. Assn.

1939 **Dutton, Loraine Orr,** 616 Mills Bldg., El Paso, Texas.
b 1898. A.B., Texas Christian U. 1917; M.S., U. Calif. 1920; M.D., U. Tenn. Med. Coll. 1931; Dir. Lab., El Paso City Co. Hospital; Allergy Serv. City Co. Hosp.; Staff, Providence and Hotel Dieu Hosps.; A.M.A.; Scuth. Med. Assn., Sec. Allergy Section, 1942; F.A.C.A.; S-W Allergy Forum; Soc. Allergy for Mycological Invest.; Texas Soc. of Path.; Editorial Board, Ann. Allergy.

1935 **Efron, Bernard Gelfand,** Pere Marquette Bldg., New Orleans, La.
b 1902. Premed. Mt. Vernon Coll. 1922; M.D., Tulane U. 1926; Sr. Assoc. Allergy Div., Touro Infirmary; A.A.A.S.; Statistical Assn.; South. Med. Assn.; A.M.A.

1938 **Ellis, Ralph Victor,** 335 Jefferson Bldg., Greensboro, N. C.
b 1893. Premed. S.W. Mo. St. Teach. Coll. 1910-1912; A.B., Leland Stanford U. 1924; A.M., 1925; U. Arts & Sci. 1926; M.D., U. Minn. 1934; St. Leo's, Wesley Long, and Piedmont Mem. Hosps.; Greensboro, N. C.; Bowman Gray Med. Sch., Winston-Salem, N.C.; F.A.C.A.

1924 **Eyermann, Charles H.,** 634 North Grand Blvd., St. Louis 3, Mo.
b 1889; M.D., St. Louis U. 1911; Cert. in Intern. Med. and in Allergy 1937; Asst. Phys. Barnes Hosp.; Phys. Allergy Clin., Washington U. Clin.; Phys., Gen. Staff, and Assoc. Phys., Ward Serv. Jewish Hosp.; Consult. Phys. City Hosp.; Instr. Med. Washington U.; A.M.A.; M., St. Louis Soc. Intern. Med.; Sec. Allergy Clin. and Round Table South. Med. Assn. 1935-1936, Sec. Section Allergy South. Med. Assn., 1937, Vice Chm., 1938, Chm., 1939; Pres., A. Assn. Study Allergy, 1937-1938.

1924 **Famulener, Lemuel William,** 275 Engle St., Englewood, N. J.
b 1875. Ph.C., U. Mich. 1900; A.B., 1903; M.D., 1906; Retired; F.A.A.A.S.; N.Y. Acad. Med.; M., A. Assn. Path. and Bact.; A. Genetic Assoc.; N.Y. Path. Soc.; Soc. Am. Bacteriol.

1938 **Farmer, Laurence,** 950 Park Ave., New York 28, N. Y.
b 1895. Premed. Hohenzollern Gymnasium, Berlin, Germany, 1915; M.D., U. Berlin 1920; Assoc. Att. Phys., Chief Allergy Clin. Lenox Hill Hosp.; Asst. Vis. Phys. 2nd Med. (Cornell) Div., Bellevue Hosp.; Instr. Clin. Med. Cornell U.

1933 **Feinberg, Samuel M.,** 185 No. Wabash Ave., Chicago 1, Ill.
b 1895. B.S., U. Wisc. 1917; M.D., Rush 1919; Cert. in Intern. Med. 1937 and in Allergy 1942; Att. Phys. Passavant Mem. Hosp.; Assoc. Prof. Med.; Chief, Div. Allergy, Northwestern U. Med. Sch.; A.M.A.; F.A.C.P.; M., A.A.A.S.; Chicago Soc. Allergy, Vice Pres., 1934-1935, Pres., 1935-1936; Chicago Soc. Intern. Med.; A. Assn. Study Allergy, Vice Pres., 1940-1941, Pres.-elect, 1941-1942, Pres., 1942-1943.

1934 **Figley, Karl Dean,** 316 Michigan St., Toledo 2, Ohio.
b 1887; B.S., Ohio Wesleyan U. 1908; M.D., Jefferson Med. Coll. 1913; Capt., M.C., 1917-1919; Cert. in Intern. Med. and in Allergy, 1943; Att. Phys. Toledo Hosp.; A.M.A.; F.A.C.P.; A.A.A., Treas. and M., Exec. Comm., 1944, Sec., 1945.

1926 **Fineman, Abraham Harold,** 211 Central Park W., New York 24, N. Y.
b 1896. B.S., Coll. City N.Y. 1916; M.D., Columbia U. 1920; Att. Allergy Sydenham Hosp.; F.A.C.P.

1940 **Forman, Jonathan,** 956 Bryden Road, Columbus 5, Ohio.
b 1887. A.B., Ohio State U. 1910; M.D., Starling-Ohio 1913; Cert. in Intern. Med. 1936 and in Allergy 1936; Grant Hosp., Visiting Hosp., Lect. Med. Allergy Ohio State U.; A.M.A.; F.A.C.A.; Honorary M., Soc. Study Allergy, Argentina; M., A. Assn. Med. History; A. Geriatric Soc.; A. Assn. Anatomists.

1944 **Friedman, Harold J.,** 10515 Carnegie Avenue, Cleveland 6, Ohio.
b 1907. A.B., Ohio State 1929; M.D., 1932.

1941 **Friedman, Townsend B.,** 104 S. Michigan Ave., Chicago 3, Ill. Lt. Comdr. M.C., A.U.S.

1940 **Fuchs, Abner M.,** 29 E. 9th St., New York 3, N. Y.
b 1901. Premed. Coll. City N.Y. 1918-1921; N.Y. U. 1921; M.D., U. Maryland 1925; Chief, Allergy Clin. and Asst. Phys., N.Y. Post Grad. Hosp.; Chief Allergy Clin. and Assoc. Phys. Metropolitan Hosp.; Asst. Phys. Welfare Hosp.; Clin. Instr. (Allergy) N.Y. Med. Coll.; Instr. Allergy, N.Y. Post Grad. Med. Sch.; A.M.A.; Assoc. A.C.P.

1942 **Furstenberg, Frank F.,** 401 Med. Arts Bldg., Baltimore, Md.
b 1905. A.B., Butler U. 1928; M.D., Indiana U. 1931; Surgeon (R) U.S. Pub. Health Service; Vis. Staff Sinai Hosp.; Instr., Med., Johns Hopkins Med. Sch.; F.A.C.A.; M., A. Pub. Health Assn.

1924 **Gay, Leslie N.,** 1114 St. Paul St., Baltimore 2, Md.
b 1891. Ph.B., Lafayette Coll. 1913; M.D., Johns Hopkins U. 1917; Cert. in Intern. Med. 1937 and in Allergy 1937; Phys., Johns Hopkins Hosp.; Staff, Church Home Infirm., Woman's, Mt. St. Agnes, and Union Mem. Hosps.; Assoc. Med., Johns Hopkins U.; F.A.M.A.; A.C.P.; A.A.A.S.; A. Assn. Immunol.; M., Advisory Committee Allergy; Past Pres., Soc. Study Asthma and Allied Cond.

1935 **Gelfand, H. Harold,** 20 Park Ave., New York 16, N. Y.
b 1897. Premed., Columbia U., 1919; M.D., U. Arkansas 1925; Asst. Vis. Phys., Chief, Dept. Allergy, Gouverneur Hosp.; Chief, Dept. Allergy, Stuyvesant Polyclinic; Asst. Att. Otolaryng., N.Y. Post Grad. Hosp.; Asst. Allergy, Roosevelt Hosp.; Dir. courses Allergy, Stuyvesant Polyclinic Post Grad. Sch.; A.M.A.; Assoc. Allergy Clinics, Greater N.Y., Internatl. Corresp. Club Allergy; M., Membership Committee N.Y. Co. Med. Soc. 1942-1943.

1937 **Glaser, Jerome,** 300 South Goodman St., Rochester 7, N. Y.
b 1898. A.B., Cornell 1919; M.D., 1923; Cert. in Ped. 1939; Att. Ped., Genesee Hosp.; Asst. Ped., Strong Memorial Hosp.; Instr. Ped. U. Rochester Sch. Med., F.A.M.A.; A.A.P.; A.C.A.; Alpha Omega Alpha; Sigma Xi.

1924 **Gorham, L. W.,** Albany Hosp., New Scotland Ave., Albany 3, N. Y.

1926 **Gottesman, Abraham,** 124 E. 39th St., New York 16, N. Y.
b 1885. Premed. City Coll. N.Y.; M.D., Columbia U. 1906.

1940 **Grolnick, Max,** 417 Ocean Ave., Brooklyn 26, N. Y.
b 1903. Premed. Columbia U.; M.D., L. I. Coll. Med. 1926; Adj. Att. Allergy Brooklyn Jewish Hosp.; Assoc. Att. Med. in charge Div. Allergy Izrael Zion Hosp.; Assoc. Allergy Clin., Coney Island Hosp.

1938 **Grove, Russell Clark,** 60 E 58th St., New York 22, N. Y.
b 1901. A.B., Roanoke Coll. 1922; M.D., Johns Hopkins 1926; Cert. in Otolaryng. 1935; Assoc. Otolaryng. and Chief, Otolaryng. Div., Allergy Clin., Roosevelt Hosp.; F., A. Acad. Otolaryng.; N.Y. Acad. Med.; A.M.A.; Johns Hopkins Surg. Soc.

1940 **Hampton, Stanley Forrest,** 708 Radcliff, St. Louis, Mo.
b 1908. A.B., Washington & Lee U. 1930; M.D., Washington U. 1934; Maj., M.C. (Air Force); Cert. in Intern. Med. 1943 and in Allergy 1944; Barnes Hosp.; Asst. Intern. Med. Washington U. Med. Sch.; F.A.C.A.; A.M.A.; M., St. Louis Med. Soc.; Mo. Med. Soc.; South. Med. Soc.

1936 **Hansel, French Keller,** 634 N. Grand Blvd., St. Louis 3, Mo.
b 1893. Premed., St. Louis U. 1913; M.D., 1918; Cert. in Otolaryng. 1925; Barnes, St. Louis Children's, and McMillan Hosps.; Assoc. Prof. Otolaryng. Washington U.; A.M.A.; A. Acad. Ophth. and Otolaryng.; A. Laryngol. Soc.; F.A.C.A.; Pres., 1944-1945.

1940 **Hansen-Pruss, Oscar Carl Edward,** Duke Hosp., Durham, N. C.
b 1900. A.B., Universidad Mayer de Sn Marcos, Lima, Peru, 1919; M.D., Johns Hopkins 1924; Cert. in Intern. Med. and in Allergy 1937; Assoc. Phys. and Chief, Clin. of Allergy and Hematology, Duke Hosp.; Vis. Phys. Watts Hosp.; Assoc. Prof. Med., Head of Div. Clin. Microscopy Duke U.; F.A.C.A.; A.M.A.; M., South. Med. Assn.; Internatl. Corresp. Club of Allergy.

1925 **Harkavy, Joseph,** 1165 Park Ave., New York 28, N. Y.
b 1890. A.B., Coll. City of N.Y. 1910; M.D., Cornell U. 1914; Cert. in Intern. Med. and in Allergy 1937; Chief, Allergy Div., and Assoc. Med. Mt. Sinai Hosp.; Assoc. Phys., Montefiore Hosp.; Assoc. Med., Columbia U.; F.A.M.A.; N.Y. Acad. Med.; Honorary Member, Sociedad Para el Estudio de la Alergia, Buenos Aires, Arg.; M., Soc. Exp. Biol. and Med.; Soc. Invest. Derm.; Harvey Soc.

1940 **Harris, Leonard H.,** Elyria Sav. and Trust Bldg., Elyria, Ohio.
b 1905. B.M., Northwestern U. 1932; M.D., 1933; Lt., M.C., U.S.N.R.; Cleveland City and Elyria Memorial Hosps.; A.M.A.; M., Cleveland Allergy Soc., Past Pres. and Sec.-Treas., 1939-1940.

1941 **Harsh, George Frederick,** 2001 4th Ave., San Diego 1, Calif.
b 1897. A.B., U. Ill. 1922; M.D., Rush 1931; Lt. Comdr., M.C., U.S.N.R.; U.S.N. Hosp., San Diego; Sr. Att. Phys. Mercy Hosp.; Att. Phys. San Diego Co. Hosp.; A.M.A.; F.A.C.A.; M., A.C.P.

1925 **Hebald, Selian,** 111 E. 88th St., New York 28, N. Y.
b 1895. Premed. Coll. City N.Y.; M.D., Columbia U. 1919; Assoc. Phys. and Chief Allergy Clin., Hosp. Joint Dis.; Asst. Chief, Allergy Clin., Roosevelt Hosp.; F., N.Y. Acad. Med.; M., A.C.P.

1928 **Herman, Nathan Bernard,** 1041 St. Paul St., Baltimore 2, Md.
b 1893. A.B., Johns Hopkins U. 1914; M.D., 1918; Civ. Consult. A.U.S.; Cert. in Intern. Med. 1937 and in Allergy 1941; Asst. Vis. Phys. Johns Hopkins Hosp.; Vis. Staff Union Memorial Hosp. and Hosp. Women of Md.; Consult. Med. Presbyterian Eye & Ear Hosp.; Assoc. Med., Sch. Med., Johns Hopkins U.; A.M.A.; F.A.C.P.

1935 **Hill, Lewis Webb,** 23 St. Johns St., Boston, Mass.
b 1889. A.B., Harvard 1909; M.D., 1913; Lt. Col., M.C., A.U.S.; Cert. in Ped. 1933; Vis. Phys. Children's Hosp., Boston; Assoc. Ped. Harvard U. Med. Sch.; M., A. Ped. Soc.; A.A.P., M., Exec. Bd., 1938 to date; A.M.A.

1924 **Hooker, Sanford Burton,** 78 E. Concord St., Boston 18, Mass.
b 1888. A.B., Dartmouth 1909; A.M., U. Calif. 1916; Ch.B., Boston U. 1912; M.D., 1913; Lt., M.R.C., 1917-1919; M., Evans Memorial; Immunologist, Mass. Memorial Hosp.; Prof. Immunol., Boston U. Sch. Med.; F., A. Assoc. Immunol., Pres., 1936-1937; A.C.A. (Hon.); A.A.A.S.; A.M.A.; A. Pub. Health Assn.; Soc. A. Bact.; Soc. Exp. Biol. and Med.; Pres., Soc. Study Asthma and Allied Cond., 1935-1936.

1931 **Huber, Harry Lee,** 122 S. Michigan Ave., Chicago 3, Ill.
b 1883. B.S., U. Chicago, 1913; M.S., 1915; Ph.D., 1917; M.D., Rush Med. Sch. 1918; Cert. in Intern. Med. 1937 and in Allergy 1942; M., Central Soc. Clin. Research; Pres., Soc. Study Asthma and Allied Cond. 1939; Pres., A. Assn. Study Allergy 1937.

1927 **Hurwitz, Samuel Hayman,** 490 Post St., San Francisco 2, Calif.
b 1885. A.B., Harvard U. 1907; A.M., 1908; M.D., Johns Hopkins U. 1912; Cert. in Intern. Med. 1937; Phys. in charge Allergy Clin. Stanford U. Med. Sch. and Hosp.; Clin. Prof. Med., Stanford U.; F.A.M.A.; A.C.P.; A.C.A.

1924 **Kahn, Isidore Stanley,** 1708 Nix Bldg., San Antonio 5, Tex.
b 1879. B.A., Harvard 1900; M.D., 1904; Cert. in Intern. Med. and in Allergy 1937; Vis. Phys., Nix Hosp.; F.A.M.A.; South. Natl. T.B.; A.C.P.

1941 **Kaplan, Morris Aaron,** 5240 Sheridan Rd., Chicago 40, Ill.
b 1907. Premed., Crane Jr. Coll., Lewis Inst., Chicago; B.S., 1929; M.S., 1931; M.D., U. Ill. 1932; Lt., M.C., U.S.N.R. Navy Epidemiol.; Research Educ. Hosp. U. Ill.; Edgewater Hosp.; A.M.A.; M., Sigma Xi, Chicago Soc. Allergy; Assn. Mil. Surg. of U. S.

1940 **Keeney, Edmund Ludlow,** 1201 North Calvert St., Baltimore 2, Md.
b 1908. A.B., U. Ind. 1930; M.D., Johns Hopkins U. 1934; Asst. Vis. Phys. Johns Hopkins Hosp.; Instr. Med. Johns Hopkins U.

1924 **Kern, Richard A.,** 1239 Remington Rd., Wynnewood, Pa.
b 1891. A.B., U. Pa. 1910; M.D., 1914; Capt., M.C., U.S.N.R.; Cert. in Intern. Med. 1936 and in Allergy 1936; Vis. Phys. and Chief Med. O.P. Dept. and Allergy Section, Hosp. of U. Pa.; Prof. Clin. Med., Sch. Med. and Grad. Sch. Med., U. Pa.; F.A.C.P.; M., Assn. A. Phys.; A. Soc. Clin. Invest.; M. and Past Pres., A. Clin. and Climat. Assn.; Assn. Mil. Surg.; Phila. Path. Soc.; M. and Past Pres., Phila. Allergy Soc.; A.C.P.; Phila. Physiol. Soc.; A.M.A.; Sigma Xi, Alpha Omega Alpha, Phi Chi, Phi Gamma Delta; Past Pres., Soc. Study Asthma and Allied Cond.; Past Pres., A Assoc. Study Allergy.

1942 **Kibler, Charles Samuel,** 110 S. Scott St., Tucson, Ariz.
b 1889. B.S., U. Chicago 1912; M.D., Rush Med. 1914; Capt., M.C., World War I; Cert. in Intern. Med. 1937; Govern. Staff, St. Mary's Hosp.; F., A. Coll. Chest Phys.; A. Heart Assn.; A.C.P.

1927 **King, Donald S.,** 1101 Beacon St., Brookline, Mass.

1932 **Lamson, Robert Ward,** 1930 Wilshire Blvd., Los Angeles 5, Calif.
b 1889. B.Sc., Mass. State Coll. 1912; M.A., Columbia U. 1914; Ph.D., Harvard U. 1922; M.D., 1925; Cert. Intern. Med. 1937; Assoc. Staff Good Samaritan Hosp.; Sr. Vis. Phys., Santa Fe Coast Lines Hosp. Assn.; In charge Allergy Clin., Eye, Ear, Nose and Throat Hosp.; F.A.C.P.; A.M.A.; A. Assoc. Immunol.; Soc. Exp. Biol. and Med.

1924 **Leopold, Simon S.,** 255 S. 17th St., Philadelphia 3, Pa.
b 1892. Premed., U. Pa.; M.D., 1914; Lt., M.C., World War I; Chief Thoracic Clin., Vis. Ward Phys. Hosp. U. Pa.; Asst. Prof. Med.; Head of Dept. Phys. Diag. U. Pa.; F.A.C.P.; Phila. Coll. Phys.; M., Phila. Allergy Soc., Pres., 1944; A.M.A.

1944 **Levin, Samuel Jonah,** 469 Fisher Building, Detroit 2, Mich.
b 1900. M.D., U. Toronto, 1923; Lt. Comdr., M.C., U.S.N.R.; Cert. in Ped. 1935; Chief Allerg. Clin. Children's Hosp.; Att. Staff Grace Hosp.; Instr. Ped. and Allerg., Wayne U. Coll. Med.; F.A.M.A.; A.C.A.; A.C.P.

1925 **Levine, Philip,** 35 Elizabeth Ave., Linden, N. J.
b 1900. M.S., Coll. City N.Y. 1919; M.D., Cornell U. 1923; M., N.Y. Acad. Med.; Harvey Soc.; A. Assn. Immunol.; Soc. Exp. Biol. and Med.; A. Soc. Clin. Path.; Sigma Xi, Soc. Naturalists; A.M.A.; N.Y. Acad. Sc.; Bd. of Med. Control of Blood Transfusion Assn. 1936.

1938 **Loveless, Mary E.,** 31 Beekman Place, New York 21, N. Y.
b 1899. A.B., Stanford U. 1921; M.D., 1925; Asst. Prof. Med., Cornell U. Med. Coll.; Dir., Allergen and Research Lab.; Phys. O.P.D., Dept. Med., N.Y. Hosp.; F.A.M.A.; N.Y. Acad. Med.

1929 **Mac Innis, E. Katharine Baylis,** 1515 Bull St., Columbia 49, S. C.
b 1902. B.S., U. S. Carolina 1923; M.D., Woman's Med. Coll. of Pa. 1926; Allergy Section, Columbia and Providence Hosps.; F.A.M.A.; M., A. Med. Women's Assn.

1924 **Mc Laughlin, James Stephen,** 334 S. 21st St., Philadelphia, Pa.
b 1895. Jefferson Premed. Coll. 1916; M.D., Jefferson Med. Coll. 1920; Cert. in Intern. Med. 1942 and in Allergy 1942; Chief Allergy Clin. and Asst. Phys. Pa. Hosp.; Clin. Asst. Dept. Allergy, Jefferson Hosp.; Asst. Phys. Med., Germantown Hosp.; F.A.M.A.; Coll. Phys. Phila.; M., Phila. Allergy Soc., Pres., 1940.

1932 **Mac Quiddy, Ernest Lynn,** 478 Aquila Court Bldg., Omaha 2, Neb.
b 1889. A.B., Park Coll. Mo. 1914; M.D., U. Neb. 1921; Chief Staff Booth Memorial Hosp.; Methodist, and U. Neb. Hosps.; Assoc. Prof. Med. U. Neb.; F.A.C.P.; A.M.A.

1935 **Markow, Harry,** 881 Park Place, Brooklyn 16, N. Y.
b 1895. Premed., N.Y.U.; M.D., U. and Bellevue Hosp. 1918; Att. Phys. and Chief Allergy Clin., Beth-El Hosp.; A.M.A.

1927 **Maytum, Charles Koran,** Mayo Clinic, Rochester, Minn.
b 1895. Premed. U. S. Dakota 1915; M.D., U. Iowa 1919; Lt. Col., M.C., A.U.S.; Cert. in Intern. Med. and in Allergy 1941; F.A.C.P.; A.M.A.; M., Alumni Assn. Mayo Foundation.

1924 **Menagh, Frank R.,** Henry Ford Hosp., Detroit 2, Mich.

1925 **Mersereau, William J.,** 102 E. 75th St., New York 21, N. Y.

1924 **Meyer, George P.,** 410 Haddon Ave., Camden, N. J.

1924 **Miller, Hyman,** 123 N. San Vicente Blvd., Beverly Hills, Calif.
b 1897. A.B., Stanford U. 1918; M.D., 1922; Cert. in Intern. Med. and in Allergy 1937; Chief Allergy Serv., Los Angeles Gen. Hosp.; Assoc. Att. Serv., Cedars of Lebanon Hosp., Courtesy Staff, Good Samaritan, and Children's Hosps.; Asst. Clin. Prof. Med., U. South. Calif.; F.A.M.A.; A.C.A.; M., A. Assn. Study History Med.

1935 **Miller, Merle M.,** 6013 Greene St., Philadelphia, Pa.

1935 **Nelson, Tell,** 636 Church St., Evanston, Ill.
b 1899. B.S., U. Chi. 1920; M.D., Rush Med. Coll. 1923; Lt. Col., M.C., A.U.S.; F.A.M.A.; A.C.A.; Chi. Allergy Soc., Past Pres.; A. Ther. Soc.; Inst. Med.; Honolulu Med. Soc.

1930 **O'Keefe, Edward Scott,** 31 Broad St., Lynn, Mass.
b 1886. A.B., Harvard 1907; M.D., 1911; Cert. in Ped. 1943; Mass. Gen. Hosp.; Instr. Ped. Harvard U.

1936 **Osgood, Howard,** 187 Linwood Ave., Buffalo 8, N. Y.
b 1889. A.B., cum laude, in Chem., Harvard 1911; M.D., 1917; Cert. in Intern. Med. 1937 and in Allergy 1939; Asst. Att. Phys., Chief Allergy Clin., Buffalo Gen. Hosp.; Acting Chief, Allergy Clin., Buffalo Children's Hosp.; Asst. Prof. Med. U. Buffalo; F.A.C.P.; A.M.A.; Alpha Omega Alpha; Chm. Section Med., Buffalo Acad. Med., 1922 and 1932.

1923 **Paddock, Royce,** 965 Broad Street, Newark 2, N. J.
b 1889. A.B., Columbia 1910; M.D., 1914; Att. Phys. Allergy; Chief, Dept. Allergy, St. Barnabas Hosp.

1935 **Parsons, John P.,** U.S. Naval Hosp., Portsmouth, Va.
b 1904. A.B., Johns Hopkins 1925; M.D., 1930; Lt. Comdr., M.C., U.S.N.R.; Asst. Vis. Phys. Johns Hopkins Hosp.; Instr. in Med. Johns Hopkins U.; Assoc. M. A. Coll. Phys.

1931 **Peck, Samuel M.,** 1936 Park Road N. W., Washington, D. C.
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(To be continued.)